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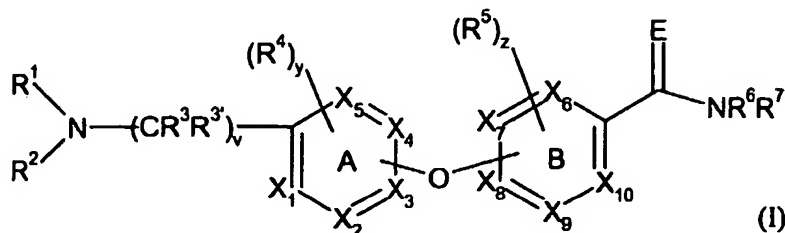
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[Continued on next page]

(54) Title: DIARYL ETHERS AS OPIOID RECEPTOR ANTAGONIST



(57) Abstract: A compound of the formula (I) wherein the variables  $X_1$  to  $X_{10}$ ,  $R^1$  to  $R^7$  including  $R^3$ , E, v, y, z, A and B are as described, or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixtures thereof, useful for the treatment, prevention or amelioration of obesity and Related Diseases is

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disclosed.



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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ,

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**DIARYL ETHERS AS OPIOID RECEPTOR ANTAGONIST**

The present invention is in the field of medicinal chemistry. The invention relates specifically to compounds useful as opioid antagonists, methods of treatment, methods of using, and pharmaceutical compositions thereof.

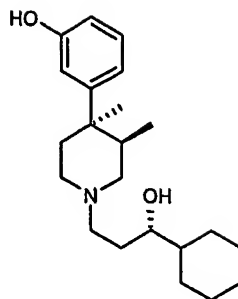
**Background**

Three types of opioid receptors, mu, kappa, and delta opioid receptors are generally reported. Recent evidence points to the interactions between receptor dimer combinations of mu, kappa and/or delta receptors (called heterodimers) as also contributing to opioid activity. Opioid receptors and their normal regulation or lack thereof, has been implicated in disease states including irritable bowel syndrome, nausea, vomiting, pruritic dermatoses, depression, smoking and alcohol addiction, sexual dysfunction, stroke and trauma in animals. Therefore it is not surprising that the ability to antagonistically bind opioid receptors has been shown to produce ameliorative, preventative and/or treatment effects in animals including humans afflicted with one or more of these disease states.

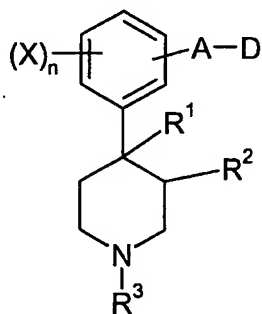
More recently, certain antagonists of the opioid receptors have been found to increase metabolic energy consumption, and reduction of weight in obese rats while maintaining muscle mass. These findings indicate that an effective opioid antagonist may be useful in preventing, treating and/or ameliorating the effect of obesity. Considering the percentage of the population that is obese in Western societies and the indirect costs associated with treating the effects and symptoms of obesity and Related Diseases, the importance of these findings cannot be overstated.

Though many opioid antagonists have been disclosed, the search continues for alternative and/or improved or more effective antagonists having an overall benefit to the patient with little or no major side effects. U.S. Patent No. 4,891,379 disclosed phenylpiperidine opioid antagonists useful for the treatment of diabetes and obesity. In particular, U.S. patent 4,891,379 disclosed the compound LY 255582 represented by the structure:

2



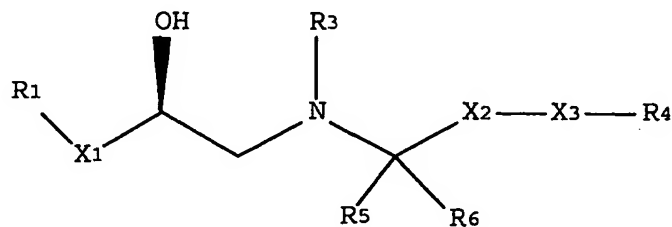
U.S. Patent No. 4,191,771 also disclosed compounds useful as opioid antagonists. Also, bicyclic analogs of phenyl piperidine have been prepared and reported as opioid antagonists in Wentland, et al., *Biorganic and Medicinal Chemistry Letters* 11 (2001) 623-626; see also Wentland, et al., *Bioorganic and Medicinal Chemistry Letters* 11 (2001) 1717-1721. Finally, European Patent application number EP 1 072592A2 filed May 18, 2000, discloses phenylpiperidine compounds of formula 1



1

wherein A, D, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X, and n have meanings given in the description, which are useful in the prophylaxis and in the treatment of diseases mediated by opioid receptors such as pruritus.

U.S patent No. 6,140,352 and related patents disclose the compound of formula Formula 1



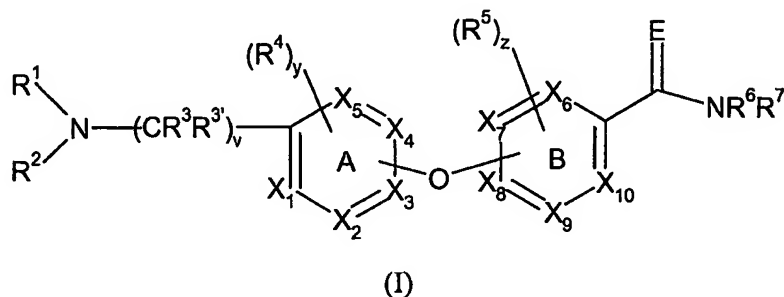
(1)

wherein the variables  $X_1$ ,  $X_2$ ,  $X_3$ ,  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are as described therein, as agonists of the beta adrenergic receptor useful for the treatment of diabetes and obesity.

Regardless of these and other disclosures of compounds useful as opioid receptor antagonists, or useful for the treatment of obesity, and/or diabetes by other mechanisms, there remains an unmet medical need for a safe, effective and/or alternate treatment or prophylaxis of diseases associated with opioid receptors, particularly obesity and Related Diseases.

### Summary of the Invention

The present invention provides a compound of the formula (I)



wherein

each of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ ,  $X_7$ ,  $X_8$ ,  $X_9$  and  $X_{10}$  is C, CH, or N; provided that each of rings A or B has no more than 2 nitrogen atoms;

E is O or NH;

v is 1, 2, or 3;

$R^1$  and  $R^2$  are independently selected from hydrogen,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl, aryl,  $C_3$ - $C_8$  cycloalkyl,  $-C_1$ - $C_{10}$  alkylaryl, heterocyclyl,  $-C_1$ - $C_{10}$  alkylheterocyclic, -arylheterocyclyl,  $-C_3$ - $C_8$  cycloalkylheterocyclyl,  $-C_1$ - $C_8$  alkylC(O) $C_1$ - $C_8$  alkyl, aryl C(O) $C_1$ - $C_8$  alkyl-,  $C_3$ - $C_8$  cycloalkylC(O)( $CH_2$ ) $n$ -,  $-C_2$ - $C_8$  alkylCH(OH)aryl,  $-C_2$ - $C_8$  alkylCH(OH)cycloalkyl,  $-C_2$ - $C_8$  alkylCH(OH)heterocyclyl  $C_2$ - $C_8$  alkylCH(OH)aryl,  $-C_1$ - $C_8$  alkylC(O)heterocyclic,  $-C_1$ - $C_8$  alkylC(O)aryl, aryloxy $C_1$ - $C_8$  alkyl-, benzhydryl, fused bicyclic,  $C_1$ - $C_8$  alkylfused bicyclic, phenylC(O)-, phenylC(O)  $C_1$ - $C_8$  alkyl-,  $C_1$ - $C_8$  alkoxy $C_1$ - $C_8$  alkyl-,  $-CO(O)C_1$ - $C_8$ alkyl,  $-SO_2C_1$ - $C_8$ alkyl,  $-SO_2C_1$ - $C_{10}$  alkylaryl,  $-SO_2C_1$ - $C_8$  alkylheterocyclic,  $-C_1$ - $C_8$  alkylcycloalkyl,  $-(CH_2)_nC(O)OR^8$ ,  $-(CH_2)_nC(O)R^8$ ,  $-(CH_2)_mC(O)NR^8R^8$ , and  $-(CH_2)_mNSO_2R^8$ ; wherein each of the alkyl, alkenyl, cycloalkyl, heterocyclic, and aryl groups are optionally substituted with one to five groups

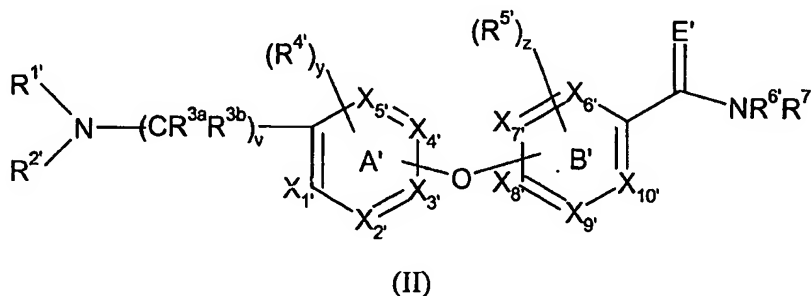
independently selected from halo, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylaryl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylheterocyclic, -C<sub>1</sub>-C<sub>8</sub> alkylcycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>C(O)OR<sup>8</sup>, -(CH<sub>2</sub>)<sub>n</sub>C(O)R<sup>8</sup>; and wherein R<sup>1</sup> and R<sup>2</sup> may optionally combine with each other, or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen-containing heterocycle which nitrogen-containing heterocycle may further have substituents selected from the group consisting of amino, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, halo, oxo, C<sub>1</sub>-C<sub>8</sub> haloalkyl; and wherein R<sup>1</sup> and R<sup>2</sup> may independently attach to the A ring to form a 4, 5, 6, or 7-member nitrogen-containing bicyclic heterocycle which nitrogen-containing bicyclic heterocycle may further have substituents selected from the group consisting of oxo, amino, -C<sub>1</sub>-C<sub>8</sub> alkyl, -C<sub>2</sub>-C<sub>8</sub> alkenyl, -C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, halo, and C<sub>1</sub>-C<sub>8</sub> haloalkyl; and wherein R<sup>1</sup> and R<sup>2</sup> are not simultaneously hydrogen; and provided that when v is 2, and R<sup>3</sup> and R<sup>3'</sup> are both hydrogen or CH<sub>3</sub>, and both A and B rings are phenyl, then the group -NR<sup>1</sup>R<sup>2</sup> is not equal to -NHCH<sub>2</sub>Phenyl; and further provided that when one of R<sup>1</sup> or R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A and B rings are phenyl, then R<sup>6</sup> and R<sup>7</sup> are not simultaneously hydrogen; R<sup>3</sup> and R<sup>3'</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylcycloalkyl, and -C<sub>1</sub>-C<sub>8</sub> alkylaryl; R<sup>4</sup> and R<sup>5</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, -C<sub>2</sub>-C<sub>8</sub> alkynyl, -C<sub>1</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, halo, C<sub>1</sub>-C<sub>8</sub> haloalkyl, -C<sub>1</sub>-C<sub>8</sub> alkoxyhaloalkyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub> alkyl, -C<sub>1</sub>-C<sub>8</sub> alkylamino, -C<sub>1</sub>-C<sub>8</sub> alkylcycloalkyl, -(CH<sub>2</sub>)<sub>m</sub>C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, and (CH<sub>2</sub>)<sub>n</sub>NR<sup>8</sup>R<sup>8</sup>, wherein each R<sup>4</sup> or R<sup>5</sup> is attached to its respective ring only at carbon atoms, and wherein y is 0, 1, 2, or 3; and wherein z is 0, 1, 2, or 3; R<sup>6</sup> and R<sup>7</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub> alkoxy, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkyl, SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylaryl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub> alkylheterocyclic, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, -C<sub>1</sub>-C<sub>6</sub> alkylcycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>C(O)R<sup>8</sup>, -(CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>8</sup>R<sup>8</sup>, and -(CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>R<sup>8</sup>; wherein each of the alkyl, alkenyl, and aryl groups are optionally substituted with one to five groups

independently selected from C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, aryl, and C<sub>1</sub>-C<sub>8</sub> alkylaryl; and wherein R<sup>6</sup> and R<sup>7</sup> may independently combine with each other, and with the nitrogen atom to which they are attached or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen containing heterocycle which nitrogen containing heterocycle may optionally have substituents selected from the group consisting of oxo, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, -C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, -CO(O)C<sub>1</sub>-C<sub>8</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub> alkoxy, -C<sub>1</sub>-C<sub>8</sub> alkylamine, amino, halo, and haloalkyl;

R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>1</sub>-C<sub>8</sub> alkylaryl, -C(O)C<sub>1</sub>-C<sub>8</sub> alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub> alkyl; and wherein n is 0, 1, 2, 3 or 4 and m is 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

The present invention also provides a method for the prevention, treatment and/or amelioration of the symptoms of obesity and Related Diseases comprising administering a therapeutically effective amount of a compound of formula II to a patient in need thereof wherein formula II is represented by the structure



wherein

each of X<sub>1</sub>', X<sub>2</sub>', X<sub>3</sub>', X<sub>4</sub>', X<sub>5</sub>', X<sub>6</sub>', X<sub>7</sub>', X<sub>8</sub>', X<sub>9</sub>' and X<sub>10</sub>' is C, CH, or N; provided that each of rings A' or B' has no more than 2 nitrogen atoms;

E' is O or NH;

v is 0, 1, 2 or 3;

R<sup>1</sup>' and R<sup>2</sup>' are independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -C<sub>1</sub>-C<sub>10</sub> alkylaryl, heterocyclyl, -C<sub>1</sub>-C<sub>10</sub> alkylheterocyclic, -arylheterocyclyl, -C<sub>3</sub>-C<sub>8</sub> cycloalkylheterocyclyl, -C<sub>1</sub>-C<sub>8</sub> alkylC(O)C<sub>1</sub>-C<sub>8</sub> alkyl, aryl C(O)C<sub>1</sub>-C<sub>8</sub> alkyl-, C<sub>3</sub>-C<sub>8</sub> cycloalkylC(O)(CH<sub>2</sub>)<sub>n</sub>-, -C<sub>2</sub>-C<sub>8</sub> alkylCH(OH)aryl, -C<sub>2</sub>-C<sub>8</sub> alkylCH(OH)cycloalkyl, -C<sub>2</sub>-C<sub>8</sub> alkylCH(OH)heterocyclyl, -C<sub>2</sub>-C<sub>8</sub> alkylCH(OH)aryl, -

$C_1-C_8$  alkylC(O)heterocyclic,  $-C_1-C_8$  alkylC(O)aryl, aryloxy $C_1-C_8$  alkyl-, benzhydryl, fused bicyclic,  $C_1-C_8$  alkylfused bicyclic, phenylC(O)-, phenylC(O)  $C_1-C_8$  alkyl-,  $C_1-C_8$  alkoxy $C_1-C_8$  alkyl-,  $-CO(O)C_1-C_8$ alkyl,  $-SO_2C_1-C_8$ alkyl,  $-SO_2C_1-C_{10}$  alkylaryl,  $-SO_2C_1-C_8$  alkylheterocyclic,  $-C_1-C_8$  alkylcycloalkyl,  $-(CH_2)_nC(O)OR^8$ ,  $-(CH_2)_nC(O)R^8$ ,  $-(CH_2)_mC(O)NR^8R^8$ , and  $-(CH_2)_mNSO_2R^8$ ; wherein each of the alkyl, alkenyl, cycloalkyl, heterocyclic, and aryl groups are optionally substituted with one to five groups independently selected from halo,  $C_1-C_8$  haloalkyl,  $C_1-C_8$  thioalkyl,  $C_1-C_8$  alkyl,  $C_2-C_8$  alkenyl, aryl,  $-C_1-C_8$  alkylaryl,  $-C(O)C_1-C_8$  alkyl,  $-CO(O)C_1-C_8$  alkyl,  $-SO_2C_1-C_8$  alkyl,  $-SO_2C_1-C_8$  alkylaryl,  $-SO_2C_1-C_8$  alkylheterocyclic,  $-C_1-C_8$  alkylcycloalkyl,  $-(CH_2)_nC(O)OR^8$ ,  $-(CH_2)_nC(O)R^8$ ; and wherein  $R^{1'}$  and  $R^{2'}$  may optionally combine with each other, or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen-containing heterocycle which nitrogen-containing heterocycle may further have substituents selected from the group consisting of amino,  $C_1-C_8$  alkyl,  $C_2-C_8$  alkenyl,  $C_2-C_8$  alkynyl, aryl,  $C_1-C_8$  alkylaryl,  $-C(O)C_1-C_8$  alkyl,  $-CO(O)C_1-C_8$  alkyl, halo, oxo,  $C_1-C_8$  haloalkyl; and wherein  $R^{1'}$  and  $R^{2'}$  may independently attach to the A' ring to form a 4, 5, 6, or 7-member nitrogen-containing bicyclic heterocycle which nitrogen-containing bicyclic heterocycle may further have substituents selected from the group consisting of oxo, amino,  $-C_1-C_8$  alkyl,  $-C_2-C_8$  alkenyl,  $-C_2-C_8$  alkynyl, aryl,  $-C_1-C_8$  alkylaryl,  $-C(O)C_1-C_8$  alkyl,  $-CO(O)C_1-C_8$  alkyl, halo, and  $C_1-C_8$  haloalkyl; provided that  $R^{1'}$  and  $R^{2'}$  are not simultaneously hydrogen; and provided that when v is 2, and  $R^{3a}$  and  $R^{3b}$  are both hydrogen or  $CH_3$ , and both A' and B' rings are phenyl, then the group  $-NR^{1'}R^{2'}$  is not equal to  $-NHCH_2$ Phenyl; and further provided that when one of  $R^{1'}$  or  $R^{2'}$  is  $-CH_2CH_2$ -optionally substituted phenyl or  $-CH_2CH_2$ -optionally substituted naphthyl, or  $-CH_2CH_2$ -optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A' and B' rings are phenyl, then  $R^{6'}$  and  $R^{7'}$  are not simultaneously hydrogen;

$R^{3a}$  and  $R^{3b}$  are each independently selected from hydrogen,  $C_1-C_8$  alkyl,  $C_2-C_8$  alkenyl,  $C_2-C_8$  alkynyl, aryl,  $-C_1-C_8$  alkylcycloalkyl, aryl, and  $-C_1-C_8$  alkylaryl;

$R^{4'}$  and  $R^{5'}$  are each independently selected from hydrogen,  $C_1-C_8$  alkyl,  $C_2-C_8$  alkenyl,  $C_2-C_8$  alkynyl,  $-C_1-C_8$  alkoxyalkyl,  $C_1-C_8$  thioalkyl, halo,  $C_1-C_8$  haloalkyl,  $-C_1-C_8$  alkoxyhaloalkyl, aryl,  $-C_1-C_8$  alkylaryl,  $-C(O)C_1-C_8$  alkyl, or  $-C(O)OC_1-C_8$  alkyl,  $-C_1-C_8$  alkylamino,  $-C_1-C_8$  alkylcycloalkyl,  $-(CH_2)_mC(O)C_1-C_8$  alkyl, and  $-(CH_2)_nNR^8R^8$ ,



wherein each  $R^{4'}$  and  $R^{5'}$  is attached to its respective ring only at carbon atoms, and wherein  $y$  is 0, 1, 2, or 3; and wherein  $z$  is 0, 1, 2, or 3;

$R^{6'}$  and  $R^{7'}$  are each independently selected from hydrogen,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl,  $-C(O)C_1$ - $C_8$  alkyl, hydroxy,  $C_1$ - $C_8$  alkoxy,  $-SO_2C_1$ - $C_8$  alkyl,  $SO_2C_1$ - $C_8$  alkylaryl,  $-SO_2C_1$ - $C_8$  alkylheterocyclic, aryl,  $-C_1$ - $C_8$  alkylaryl,  $C_3$ - $C_7$  cycloalkyl,  $-C_1$ - $C_6$  alkylcycloalkyl,  $-(CH_2)_n C(O)R^8$ ,  $-(CH_2)_m C(O)NR^8R^8$ , and  $-(CH_2)_m NSO_2R^8$ ; wherein each of the alkyl, alkenyl, and aryl groups are optionally substituted with one to five groups independently selected from  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl, aryl, and  $C_1$ - $C_8$  alkylaryl; and wherein  $R^{6'}$  and  $R^{7'}$  may independently combine together, and with the nitrogen atom to which they are attached or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen containing heterocycle which nitrogen containing heterocycle may further have substituents selected from the group consisting of  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl, phenyl,  $-C_1$ - $C_8$  alkylaryl,  $-C(O)C_1$ - $C_8$  alkyl,  $-CO(O)C_1$ - $C_8$  alkyl, hydroxy,  $-C_1$ - $C_8$  alkoxy, halo, and haloalkyl;

$R^8$  is hydrogen,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_1$ - $C_8$  alkylaryl,  $-C(O)C_1$ - $C_8$  alkyl, or  $-C(O)OC_1$ - $C_8$  alkyl; wherein  $n$  is 0, 1, 2, 3 or 4 and wherein  $m$  is 1, 2 or 3;

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomers or mixtures thereof.

The present invention also provides a pharmaceutical formulation comprising a compound of formula I or II in association with a carrier, diluent and/or excipient.

The present invention also relates to a method for the treatment and/or prophylaxis of obesity and Related Diseases including eating disorders (bulimia, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression related to obesity, anxiety related to obesity, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglyceremia, hyperglycemia, hyperlipoproteinemia, substance abuse, drug overdose, compulsive behavior disorders (such as paw licking in dog), and addictive behaviors such as for example, gambling, and alcoholism, comprising administering a therapeutically effective amount of a compound of formula I or formula II or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

The present invention provides a compound of formula (I) or (II) useful for the manufacture of a medicament for the treatment, prevention and/or amelioration of symptoms associated with obesity and Related Diseases.

In another embodiment, the present invention provides a compound of formula I or II or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixtures thereof, useful as an appetite suppressant.

In another embodiment, the present invention provides a method of achieving weight loss while maintaining or minimizing the loss of lean muscle mass, comprising administering a compound of formula I or II or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixtures thereof, to a patient in need thereof.

#### **Detailed Description of the Invention**

As used herein the term "obesity" has its commonly understood meaning such as "excessively fat" and includes the clinical designation of being obese as defined in and by the medical literature and brochures of support or public health organizations. For example, *Dorland's Illustrated Medical Dictionary* (29<sup>th</sup> edition, W.B. Saunders Company, Philadelphia USA.) defines obesity as an increase in bodyweight beyond the limitation of skeletal and physical requirements, as the result of an excessive accumulation of fat in the body." Because the decision of suitability for treatment of a patient with compound(s) of the present invention to a patient is to be made by a qualified physician or care giver, the patient is inherently deemed suitable or obese by the administering caregiver.

As used herein, the term "patient" includes human and non-human animals such as companion animals (dogs and cats) and livestock animals.

The preferred patient of treatment, amelioration and/or prevention of obesity and Related Diseases is human.

The terms "treating" and "treat", as used herein, include their generally accepted meanings, *i.e.*, preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein.

The terms "ameliorating" "preventing", "prevention of", "prophylaxis", "prophylactic" and "prevent" are used herein interchangeably and refer to reducing the severity of the symptoms associated with obesity and Related Diseases in a patient afflicted with same or reducing the likelihood that the recipient of a compound of formula I or II will incur or develop any of the pathological conditions, or sequela thereof, described herein.

As used herein, the term "effective amount" is synonymous with "effective dose" and means an amount of a compound of formula I or II that is sufficient in one or more administrations for preventing, ameliorating or treating a condition, or detrimental effects thereof, herein described, or an amount of a compound of formula I that is sufficient for antagonizing the opioid receptors to achieve the objectives of the invention.

The term "pharmaceutically acceptable" is used herein as an adjective and means substantially non-deleterious to the recipient patient.

The term "Active Ingredient" as used herein means a compound of formula I or II or a combination of compounds of formula I or II or a combination of a compound of formula I or II and a co-antagonist of the opioid receptor or a combination of a compound of formula I and/or II in addition to other effective anti-obesity, weight loss or anti-diabetic agent.

The term "formulation", as in pharmaceutical formulation, or "pharmaceutical composition" is intended to encompass a product comprising the Active Ingredient (as defined supra), and the inert ingredient(s) that make up the carrier, or other components of the drug as administered, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any effective composition made by admixing a compound of the present invention and a pharmaceutical carrier. The pharmaceutical formulations of the present invention also encompass a compound of the formula I or II and a pharmaceutically acceptable co-antagonist of opioid receptors useful for the treatment and/or prevention of obesity or Related Diseases.

The term "Related Diseases" as used herein refers to such symptoms, diseases or conditions caused by, exacerbated by, induced by or adjunct to the condition of being

obese. Such diseases, conditions and/or symptoms include but are not limited to eating disorders (bulimia, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, obesity related depression, obesity related anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinemia. As used herein the terms obesity related depression and obesity related anxiety are conditions of depression and anxiety respectively, that are symptomatic of certain obese patients and possibly brought on by the awareness or self-consciousness of the condition of being obese and possibly coupled with the real or perceived reaction of acceptance or disapproval by the certain individual, individuals or the public at large. Obesity related depression or anxiety may generally be alleviated or treated as the condition of being obese is treated and/or prevented by administration of a compound of formula I or II.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

The term "mutual solvent" means a solvent that is used to dissolve sufficiently, two or more components of a reaction or mixture separately prior to reaction or mixing, that is a solvent common to more than one reagents or components of a mixture.

The term "nitrogen containing heterocycle" refers to a aromatic or non-aromatic, monocyclic or bicyclic ring system which is a 4, 5, 6, or 7-member ring containing 1, 2 or 3 nitrogen atoms in addition to the carbon atoms completing the ring size, or a combination of 1 nitrogen atom and 1, or 2 atoms selected from oxygen, and sulfur in addition to the appropriate number of carbon atoms completing the ring size. A nitrogen containing heterocycle as used here may have 0, 1, 2 or 3 double bonds.

The term "C<sub>1</sub>-C<sub>8</sub> alkyl" or C<sub>1-8</sub> alkyl" refers to and includes all groups, structural isomers and /or homologues of alkyl groups having from 1 to 8 carbon atoms. When the term C<sub>1</sub>-C<sub>8</sub> alkyl precedes or prefixes another group, the term C<sub>1</sub>-C<sub>8</sub> alkyl, only limits the number of carbon atoms in the alkyl component. For example C<sub>1</sub>-C<sub>8</sub> alkyaryl, means an aryl group having a C<sub>1</sub>-C<sub>8</sub> alkyl group substituent such that the number of carbon atoms in the group C<sub>1</sub>-C<sub>8</sub> alkylaryl is effectively the number of carbon atoms in the aryl group plus the number of carbon atoms in the C<sub>1</sub>-C<sub>8</sub> alkyl group. Similarly, the term "C<sub>1</sub>-C<sub>8</sub>

alkylcycloalkyl" refers to a cycloalkane group having a C<sub>1</sub>-C<sub>8</sub> alkyl substituent, and wherein the entire group C<sub>1</sub>-C<sub>8</sub> alkylcycloalkane may itself be a substituent attached at either the alkyl group or the cycloalkyl group to a substrate. The definition and usage applies equally to other homologues of C<sub>1</sub>-C<sub>8</sub> such as for example, C<sub>1</sub>-C<sub>7</sub>, C<sub>1</sub>-C<sub>6</sub> etc. In general, where necessary a dash (-) has been placed by certain groups that may require it to indicate the point of attachment for clarity.

The term "cycloalkane" or "cycloalkyl" means cycloalkanes having from 3 to 8 carbon atoms i.e. from cyclopropane to cyclooctane.

The term "hal" or "halo" as used herein refers to a halogen including fluorine, chlorine, bromine or iodine.

The term "haloalkane" or "haloalkyl" means haloalkanes having from 1 to 8 carbon atoms, and from 1 to 3 halogen atoms as allowed by valency considerations. Examples include chloroethyl, trifluoromethyl, 2-chloropropyl, etc.

As used herein the terms "alkenyl" refers to straight or branched carbon atoms having 1 or 2 carbon-carbon double bonds.

As used herein the terms "alkynyl" refers to straight or branched carbon atoms having 1 or 2 carbon-carbon triple bonds.

As used herein the term "alkoxy" refers to the group "O-alkyl" wherein alkyl is as defined previously.

The term "aryl" as used herein refers to compounds or groups having the Huckel 4n+2 pi electron arrangement and includes for example, phenyl, benzyl, naphthyl, tetrahydronaphthyl, benzothiophene, etc, but excludes carbazoles and other fused tricyclic ring structures.

As used herein the term "aroxy" or "aryloxy" refers to the group "O-aryl" wherein aryl is as defined previously.

As used herein the term "fused bicyclic" means a fused cycloalkane ring system wherein each ring has from 4 to 8 carbon atoms (i.e. C<sub>8</sub>-C<sub>16</sub> fusedbicyclic) and the fused ring system has from 0 to 3 bridgehead carbon atoms. One or both of the fused rings may contain zero or one double bond. Examples of fused bicyclics include but are not limited to bicyclo[2,2,1]heptyl, bicyclo[2,2,1]heptenyl.

As used herein the term "heterocyclic" or heterocyclyl" or "heterocycle" are used interchangeably and has its usual meaning and includes mono, bi or tricyclic or

spirocyclic heterocyclic groups unless otherwise specified. Heterocycles as used herein may contain 1, 2, or 3 heteroatoms selected independently from nitrogen, oxygen or sulfur, unless otherwise specified. Examples of heterocyclic groups applicable to the present invention include but are not limited to pyranyl, piparaziny, pyrrolidinyl, azapanyl, azaflorenyl, isoquinolinyl, indolinyl, thiophenyl, benzthiophenyl, oxazolyl, morphorlinyl, thiomorphorlinyl, and piperidinyl. Each of the heterocyclic groups may be substituted mono or di or as specified with for example, alkyl, cycloalkyl, aryl, among others as defined. Furthermore, substitution may be at the 1-position or heteroatom as in piperazine, pyrrolidine or at a carbon atom or both.

As used herein, the term "protecting group" refers to a groups useful for masking reactive sites in a molecule to enhance the reactivity of another group or allow reaction at another desired site or sites following which the protecting group may be removed. Protecting groups are usually used to protect or mask groups including but not limited to -OH, -NH, and -COOH. Suitable protecting groups are known to one of skill in the art and are described in *Protecting groups in Organic Synthesis*, 3<sup>rd</sup> edition, Greene, T. W.; Wuts, P.G.M. Eds., John Wiley and Sons, New York, 1999.

As used herein, the term "solvate" is a form of the compound of the invention wherein a crystal or crystals of a compound of the invention have been formed from a stoichiometric or non-stoichiometric amount of the compound of formula I or II and a solvent. Typical solvating solvents include for example, water, methanol, ethanol, acetone and dimethylformamide.

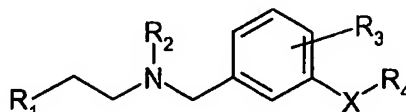
In those instances where a compound of the invention possesses acidic or basic functional groups, various salts may be formed which are more water soluble and/or more physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion-exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of

this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, hydrobromide, camsylate, carbonate, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrochloride, hydroxynaphthoate, hydroiodide, isothionate, lactate, lactobionate, laurate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate. Preferred salts for the purpose of the invention include the hydrochloride salt, the hydrobromide salt, the bisulfate salt, the methane sulfonic acid salt, the *p*-toluenesulfonic acid salt, bitartrate, the acetate and the citrate salt.

A compound of the invention as illustrated by formula I or II may occur as any one of its positional isomers, stereochemical isomers or regio- isomers, all of which are objects of the invention. Certain compounds of the invention may possess one or more chiral centers, and thus, may exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group, there exist the possibility of *cis*- and *trans*- isomeric forms of the compounds. The *R*- and *S*- isomers and mixtures thereof, including racemic mixtures as well as mixtures of enantiomers or *cis*- and *trans*- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound i.e. a chiral resolving agent. This changes the racemic form into a mixture of stereoisomers and diastereomers, because they have different melting points, different boiling points, and different solubilities and can be separated by conventional means, such as crystallization.

PCT international application WO 02/078693 A2 published October 10, 2002 discloses compounds of the formula



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and X are as described therein, as antagonists of the 5-HT<sub>6</sub> receptor for the treatment of disorders including cognitive disorders, age related disorders, mood disorders, psychosis, etc. The compounds of the present invention however, are useful for the treatment and/or prevention of obesity and Related Diseases. The compounds of the present invention have also shown inhibition of orexigenic effects, and are thus useful as appetite suppressants either as a single therapy or as combination therapy in conjunction with exercise and other effective appetite suppressing or weight loss medications.

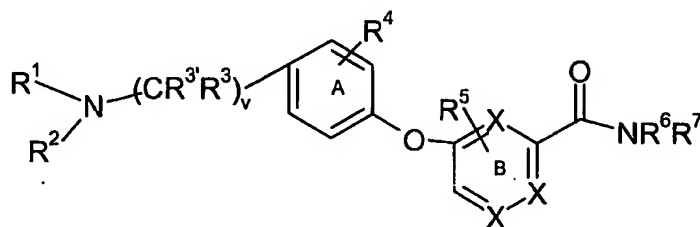
The efficacy of compounds of the present invention have been shown by their activity in several biological models including a scintillation proximity assay (SPA GTP-gamma binding assay), an opioid receptor ex-vivo binding assay, a rat obesity in-vivo assay and an indirect calorimetry assay that measures energy balance and respiratory quotient. In these models, sample compounds of the present invention performed better than or about equal to reference compounds. The primary reference compound is a highly potent former clinical trial candidate LY 255582 disclosed in U.S. patent No. 4,891,379, which development was discontinued for lack of satisfactory human oral bioavailability. Oral administration of the opioid receptor antagonist LY255582 has been shown to produce robust reductions in food intake following acute and chronic treatment in rats. Moreover, chronic treatment with LY255582 produced a sustained negative energy balance leading to a decrease in total body mass in dietary induced obese rats fed a high fat diet. Interestingly sample compounds of the present invention have been found to produce similar or better beneficial effects compared to LY255582. Also interesting is the secondary observation that tested sample compounds of the present invention performed better in our tests when compared with Naltrexone HCl®.



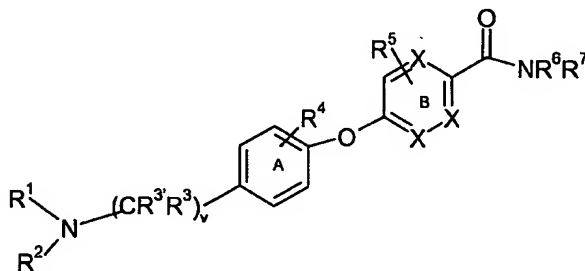
### Preferred Embodiments of the Invention

A compound of formula I preferably exists as the free base or a pharmaceutically acceptable salt. More preferred is the hydrochloride salt, the bisulfate salt, mesylate or the oxalic acid salt of the compound of formula I or II.

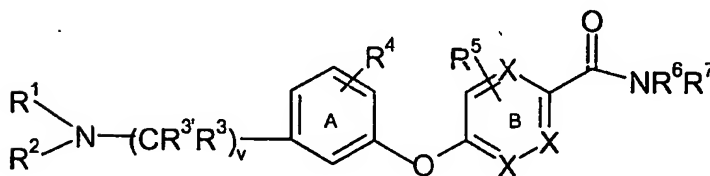
Preferred embodiments of the compound of formula I include the substructures Ia, Ib and Ic as shown below:



(Ia);



(Ib);



(Ic);

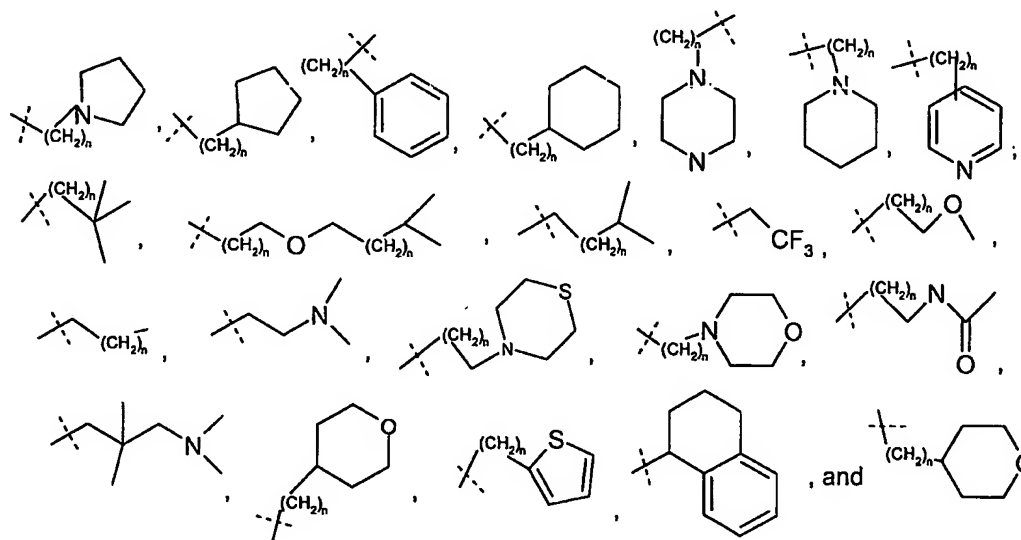
provided that  $R^1$  and  $R^2$  are not simultaneously hydrogen and provided that when  $v$  is 2, and  $R^3$  and  $R^3$  are both hydrogen or methyl, and the A ring is phenyl, the group  $-NR^1R^2$  is not equal to  $-NHCH_2Ph$ .

For the groups  $R^1$  and  $R^2$

Preferred  $R^1$  and  $R^2$  groups are independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, pentyl, phenyl, naphthyl, benzothiophene, and isopropyl provided that  $R^1$  and  $R^2$  are not simultaneously hydrogen, and provided that when  $v$  is 2,

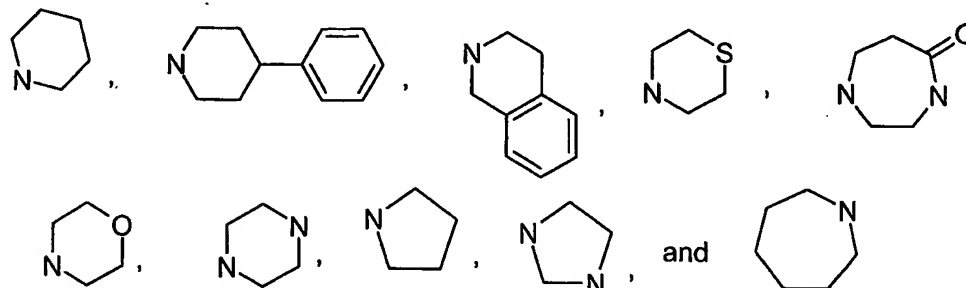
and R<sup>3</sup> and R<sup>3'</sup> are both hydrogen or CH<sub>3</sub>, and both A and B rings are phenyl, then the group -NR<sup>1</sup>R<sup>2</sup> is not equal to -NHCH<sub>2</sub>Phenyl; and further provided that when one of R<sup>1</sup> or R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A and B rings are phenyl, then R<sup>6</sup> and R<sup>7</sup> are not simultaneously hydrogen;

Also preferred are R<sup>1</sup> and R<sup>2</sup> groups independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, phenyl,



each of which is optionally substituted with a group selected from the group consisting of halogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, C<sub>1</sub>-C<sub>8</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>8</sub> alkylsubstituted phenyl, C<sub>4</sub>-C<sub>8</sub> heterocycle or -C<sub>1</sub>-C<sub>4</sub> alkylheterocycle; or combine with a group selected from C<sub>1</sub>-C<sub>8</sub> alkyl, halogen, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, C<sub>1</sub>-C<sub>8</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>8</sub> alkylsubstituted phenyl, C<sub>4</sub>-C<sub>8</sub> heterocycle or C<sub>1</sub>-C<sub>4</sub> alkyl heterocycle to form a substituted or unsubstituted bicycle or tricycle, and wherein n is preferably 1, 2, or 3; and provided that when v is 2, and R<sup>3</sup> and R<sup>3'</sup> are both hydrogen or CH<sub>3</sub>, and both A and B rings are phenyl, then the group -NR<sup>1</sup>R<sup>2</sup> is not equal to -NHCH<sub>2</sub>Phenyl; and further provided that when one of R<sup>1</sup> or R<sup>2</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A and B rings are phenyl, then R<sup>6</sup> and R<sup>7</sup> are not simultaneously hydrogen; The broken (dashed) bond indicates the point of attachment to the substrate.

Also preferred are  $R^1$  and  $R^2$  groups that combine with each other or with 1 or 2 atoms adjacent to the nitrogen atom to form a group selected from the group consisting of



each of which is optionally substituted with a group selected from the group consisting of halogen, amino,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  haloalkyl,  $C_1$ - $C_8$  thioalkyl,  $-C_1$ - $C_8$  alkylamino, phenyl,  $C_1$ - $C_8$  alkylsubstituted phenyl,  $C_4$ - $C_8$  heterocycle or  $-C_1$ - $C_4$  alkylheterocycle.

#### Preferred $R^3$ and $R^{3'}$ Groups

A preferred  $R^3$  is hydrogen. A preferred  $R^{3'}$  group is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl and benzyl.

#### Preferred $R^4$ Groups

A preferred  $R^4$  group is selected from the group consisting of hydrogen, halo,  $C_1$ - $C_5$  alkyl,  $C_1$ - $C_5$  haloalkyl,  $C_1$ - $C_5$  alkoxy,  $-C_1$ - $C_5$  alkylamino,  $-N(C_1-C_5 \text{ alkyl})_2$ ,  $-NHC_1-C_5$  alkyl,  $-C_1-C_5$  alkyl  $N(C_1-C_5 \text{ alkyl})_2$ ,  $-C_1-C_5$  alkyl  $NHC_1-C_5$  alkyl, phenyl,  $-C_1-C_5$  alkylphenyl,  $-C_1-C_5$  alkylcycloalkyl, and  $C_1$ - $C_5$  thioalkyl. More preferred is a  $R^4$  group selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, thiomethyl, phenyl, and benzyl. Most preferred is an  $R^4$  group selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, and benzyl.

Though the groups  $R^4$  and a  $R^5$  may exist as multiple substituents on their respective ring substrates, a preferred embodiment of the invention involves compounds wherein each of  $R^4$ , and  $R^5$  are independently singly or doubly substituted on their respective ring substrates.

#### Preferred $R^5$ Groups

A preferred  $R^5$  group is selected from the group consisting of hydrogen, halo,  $C_1$ - $C_5$  alkyl,  $C_1$ - $C_5$  haloalkyl,  $C_1$ - $C_5$  alkoxy,  $-C_1$ - $C_5$  alkylamino,  $-N(C_1$ - $C_5$  alkyl) $_2$ ,  $-NHC_1$ - $C_5$  alkyl,  $-C_1$ - $C_5$  alkylN( $C_1$ - $C_5$  alkyl) $_2$ ,  $-C_1$ - $C_5$  alkylNHC $_1$ - $C_5$  alkyl, phenyl,  $-C_1$ - $C_5$  alkylphenyl,  $-C_1$ - $C_5$  alkylcycloalkyl, and  $C_1$ - $C_5$  thioalkyl. More preferred is an  $R^5$  group selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, thiomethyl, phenyl, and benzyl. A most preferred  $R^5$  group is selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, and benzyl.

#### Preferred $R^6$ and $R^7$ Groups

Preferred are  $R^6$  and  $R^7$  groups independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, pentyl, isopropyl, phenyl and benzyl, provided that when one of  $R^1$  or  $R^2$  is  $-CH_2CH_2$ -optionally substituted phenyl or  $-CH_2CH_2$ -optionally substituted naphthyl, or  $-CH_2CH_2$ -optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and  $v$  is 1, and both A and B rings are phenyl, then  $R^6$  and  $R^7$  are not simultaneously hydrogen.

Also preferred are compounds of formula I wherein  $R^6$  and  $R^7$  may independently combine with each other, and with the nitrogen atom to which they are attached or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen containing heterocycle which nitrogen containing heterocycle may optionally have substituents selected from the group consisting of oxo, amino,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl, phenyl,  $-C_1$ - $C_8$  alkylaryl,  $-C(O)C_1$ - $C_8$  alkyl,  $-CO(O)C_1$ - $C_8$  alkyl, hydroxy,  $C_1$ - $C_8$  alkoxy, halo, and haloalkyl.

Most preferred are compounds of the invention wherein  $R^6$  and  $R^7$  are both hydrogen except as provided for previously.

#### Preferred E group

A most preferred E group is an oxygen atom (O).

#### Preferred A-ring

A preferred A-ring is a phenyl ring or a pyridine ring.

### Preferred B-ring

A preferred B-ring is a phenyl ring, a pyrazine ring, a pyrimidine ring or a pyridine ring. Most preferred B ring is a phenyl, pyrazine or pyridine ring.

### Preferred values for v, n and m

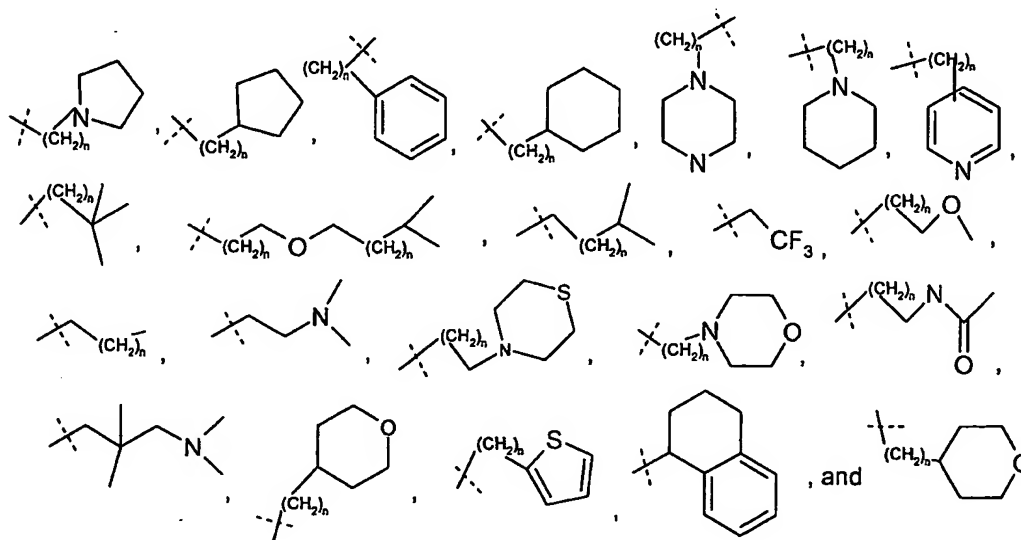
A preferred value for v is 1, or 2.

A preferred value for n is 1, 2 or 3.

A preferred value for m is 1 or 2.

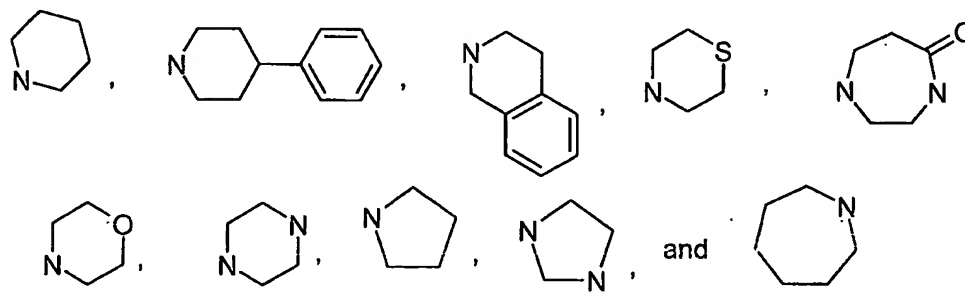
### For the groups R<sup>1'</sup> and R<sup>2'</sup>

Preferred R<sup>1'</sup> and R<sup>2'</sup> groups are independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, pentyl, and isopropyl provided that R<sup>1'</sup> and R<sup>2'</sup> are not simultaneously hydrogen, and provided that when v is 2, and R<sup>3a</sup> and R<sup>3b</sup> are both hydrogen or CH<sub>3</sub>, and both A' and B' rings are phenyl, then the group -NR<sup>1'</sup>R<sup>2'</sup> is not equal to -NHCH<sub>2</sub>Phenyl; and further provided that when one of R<sup>1'</sup> or R<sup>2'</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A' and B' rings are phenyl, then R<sup>6'</sup> and R<sup>7'</sup> are not simultaneously hydrogen; Also preferred are R<sup>1'</sup> and R<sup>2'</sup> groups independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, phenyl,



each of which is optionally substituted with a group selected from halogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, C<sub>1</sub>-C<sub>8</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>8</sub> alkylsubstituted phenyl, C<sub>4</sub>-C<sub>8</sub> heterocycle or C<sub>1</sub>-C<sub>4</sub> alkyl heterocycle; or combine with a group selected from C<sub>1</sub>-C<sub>8</sub> alkyl, halogen, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, C<sub>1</sub>-C<sub>8</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>8</sub> alkylsubstituted phenyl, C<sub>4</sub>-C<sub>8</sub> heterocycle or C<sub>1</sub>-C<sub>4</sub> alkyl heterocycle to form a substituted or unsubstituted bicycle or tricycle, and wherein n is preferably 1, 2 or 3; and and provided that when v is 2, and R<sup>3a</sup> and R<sup>3b</sup> are both hydrogen or CH<sub>3</sub>, and both A' and B' rings are phenyl, then the group -NR<sup>1'</sup>R<sup>2'</sup> is not equal to -NHCH<sub>2</sub>Phenyl; and further provided that when one of R<sup>1'</sup> or R<sup>2'</sup> is -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted phenyl or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted naphthyl, or -CH<sub>2</sub>CH<sub>2</sub>-optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and v is 1, and both A' and B' rings are phenyl, then R<sup>6'</sup> and R<sup>7'</sup> are not simultaneously hydrogen.

Also preferred are R<sup>1'</sup> and R<sup>2'</sup> groups which combine with each other or with 1 or 2 atoms adjacent to the nitrogen atom to form a group selected from the group consisting of:



each of which is optionally substituted with a group selected from the group consisting of halogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, C<sub>1</sub>-C<sub>8</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>8</sub> alkylsubstituted phenyl, C<sub>4</sub>-C<sub>8</sub> heterocycle or C<sub>1</sub>-C<sub>4</sub> alkylheterocycle.

#### Preferred R<sup>3a</sup> and R<sup>3b</sup> Groups

A preferred R<sup>3a</sup> is hydrogen. A preferred R<sup>3b</sup> group is selected from hydrogen, methyl, ethyl, propyl, isopropyl, phenyl and benzyl.

#### Preferred R<sup>4'</sup> Groups

A preferred  $R^{4'}$  group is selected from the group consisting of hydrogen, halo,  $C_1$ - $C_5$  alkyl,  $C_1$ - $C_5$  haloalkyl,  $C_1$ - $C_5$  alkoxy,  $-C_1$ - $C_5$  alkylamino,  $-N(C_1$ - $C_5$  alkyl) $_2$ ,  $-NHC_1$ - $C_5$  alkyl,  $-C_1$ - $C_5$  alkylN( $C_1$ - $C_5$  alkyl) $_2$ ,  $-C_1$ - $C_5$  alkylNHC $_1$ - $C_5$  alkyl, phenyl,  $-C_1$ - $C_5$  alkylphenyl,  $-C_1$ - $C_5$  alkylcycloalkyl, and  $C_1$ - $C_5$  thioalkyl. More preferred is a  $R^{4'}$  group selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, thiomethyl, phenyl, and benzyl. A most preferred  $R^{4'}$  group is selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, and benzyl.

Though the groups  $R^{4'}$  and  $R^{5'}$  may exist as multiple substituents on their respective ring substrates, a preferred embodiment of the invention involves compounds wherein each of  $R^{4'}$ , and  $R^{5'}$  are singly or doubly substituted on their respective ring substrates.

#### Preferred $R^{5'}$ Groups

A preferred  $R^{5'}$  group is selected from the group consisting of hydrogen, halo,  $C_1$ - $C_5$  alkyl,  $C_1$ - $C_5$  haloalkyl,  $C_1$ - $C_5$  alkoxy,  $-C_1$ - $C_5$  alkylamino,  $-N(C_1$ - $C_5$  alkyl) $_2$ ,  $-NHC_1$ - $C_5$  alkyl,  $-C_1$ - $C_5$  alkylN( $C_1$ - $C_5$  alkyl) $_2$ ,  $-C_1$ - $C_5$  alkylNHC $_1$ - $C_5$  alkyl, phenyl,  $-C_1$ - $C_5$  alkylphenyl,  $-C_1$ - $C_5$  alkylcycloalkyl, and  $C_1$ - $C_5$  thioalkyl. More preferred is an  $R^{5'}$  group selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, chloro, fluoro, trifluoromethyl, trifluoromethoxy, methoxy, ethoxy, thiomethyl, phenyl, and benzyl. A most preferred  $R^{5'}$  group is selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, and benzyl.

#### Preferred $R^{6'}$ and $R^{7'}$ Groups

Preferred are  $R^{6'}$  and  $R^{7'}$  groups independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, pentyl, isopropyl, phenyl and benzyl provided that when one of  $R^{1'}$  or  $R^{2'}$  is  $-CH_2CH_2$ -optionally substituted phenyl or  $-CH_2CH_2$ -optionally substituted naphthyl, or  $-CH_2CH_2$ -optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and  $v$  is 1, and both  $A'$  and  $B'$  rings are phenyl, then  $R^{6'}$  and  $R^{7'}$  are not simultaneously hydrogen.

Also preferred are compounds of formula II wherein  $R^{6'}$  and  $R^{7'}$  may independently combine with each other, and with the nitrogen atom to which they are attached or with 1, or 2 atoms adjacent to the nitrogen atom to form a 4, 5, 6, or 7-membered nitrogen containing heterocycle which nitrogen containing heterocycle may optionally have substituents selected from the group consisting of oxo, amino,  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl, phenyl,  $-C_1$ - $C_8$  alkylaryl,  $-C(O)C_1$ - $C_8$  alkyl,  $-CO(O)C_1$ - $C_8$  alkyl, hydroxy,  $C_1$ - $C_8$  alkoxy, halo, and haloalkyl.

Most preferred are compounds of formula II wherein  $R^{6'}$  and  $R^{7'}$  are both hydrogen provided that when one of  $R^{1'}$  or  $R^{2'}$  is  $-CH_2CH_2$ -optionally substituted phenyl or  $-CH_2CH_2$ -optionally substituted naphthyl, or  $-CH_2CH_2$ -optionally substituted 5 or 6 member monocyclic heterocyclic aromatic, and  $v$  is 1, and both  $A'$  and  $B'$  rings are phenyl, then  $R^{6'}$  and  $R^{7'}$  are not simultaneously hydrogen.

Preferred  $E'$  group

A most preferred  $E'$  group is an oxygen atom (O).

Preferred  $A'$ -ring

A preferred  $A'$ -ring is a phenyl ring or a pyridine ring.

Preferred  $B'$ -ring

A preferred  $B'$ -ring is a phenyl ring, a pyrazine ring, a pyrimidine ring or a pyridine ring. Most preferred  $B'$  ring is a phenyl, pyrazine or pyridine ring.

A preferred compound according to the present invention is a compound selected from the group consisting of:

- 6-[4-(2-Benzylamino-ethyl)-phenoxy]-nicotinamide.
- 6-{4-[2-(Benzyl-phenethyl-amino)-ethyl]-phenoxy}-nicotinamide,
- 6-(4-{2-[Benzyl-(3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,
- 6-{4-[2-(Benzyl-hexyl-amino)-ethyl]-phenoxy}-nicotinamide,
- 6-{4-[2-(Benzyl-heptyl-amino)-ethyl]-phenoxy}-nicotinamide,
- 6-(4-{2-[Benzyl-(5-methyl-hexyl)-amino]-ethyl}-phenoxy)-nicotinamide,
- 6-[4-(2-{Benzyl-[2-(3-chloro-phenyl)-ethyl]-amino}-ethyl)-phenoxy]-nicotinamide,



6-(4-{2-[Benzyl-(3-cyclohexyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[Benzyl-(3-o-tolyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[Benzyl-(3-thiophen-2-yl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(Benzyl-pentyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[Benzyl-(3-cyclopentyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-[4-(2-{Benzyl-[2-(2-fluoro-phenyl)-ethyl]-amino}-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Dibenzylamino-ethyl)-phenoxy]-nicotinamide,  
6-(4-{2-[Benzyl-(3-oxo-3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[Benzyl-(3-oxo-3-thiophen-2-yl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[Benzyl-(3-cyclohexyl-3-oxo-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[Benzyl-(3-hydroxy-3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[Benzyl-(3-hydroxy-3-thiophen-2-yl-propyl)-amino]-ethyl}-phenoxy)-  
nicotinamide,  
6-(4-{2-[Benzyl-(3-cyclohexyl-3-hydroxy-propyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(3-Phenyl-propylamino)-ethyl]-phenoxy}-nicotinamide,  
6-[4-(2-Phenethylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Hexylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Heptylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Pentylamino-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(5-Methyl-hexylamino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[2-(3-Chloro-phenyl)-ethylamino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(3-Cyclopentyl-propylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Cyclohexyl-propylamino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[2-(3-Fluoro-phenyl)-ethylamino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(3-o-Tolyl-propylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Thiophen-2-yl-propylamino)-ethyl]-phenoxy}-nicotinamide,  
6-[4-(2-Amino-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(2-Methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Chloro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3,4-Dichloro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide,

6-{4-[2-(4-Cyano-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Methyl-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3,5-Bis-trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2,6-Difluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide  
6-{4-[2-(3,5-Difluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Acetylamino-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Methyl-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Chloro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Phenoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Oxo-2,3-dihydro-1H-isoindol-1-ylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Trifluoromethoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Trifluoromethoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(Thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-[4-(2-Octylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Cyclohexylamino-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(Cyclohexylmethyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-[4-(2-Propylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Butylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Isopropylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Isobutylamino-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(3-Methyl-butylamino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(Pyridin-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Pyridin-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(5-Methyl-furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(3-Methyl-thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(5-Methyl-thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,

6-(4-{2-[(Thiophen-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-[4-(2-Ethylamino-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(4-Hydroxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Hydroxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Phenyl-prop-2-ynylamino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(Furan-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Benzofuran-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(5-Ethyl-furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(5-Chloro-thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(4-Chloro-1-methyl-1H-pyrazol-3-ylmethyl)-amino]-ethyl}-phenoxy)-  
nicotinamide,  
6-(4-{2-[(Thiazol-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(2-Methyl-1H-imidazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(3,5-Di-tert-butyl-4-hydroxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Phenoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Chloro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Cyano-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Methyl-benzylamino)-ethyl]-phenoxy}-nicotinamide.  
6-(4-{2-[(1H-Imidazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Pyridin-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(2-Phenoxy-ethylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Fluoro-4-hydroxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(2-Butyl-1H-imidazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Benzo[b]thiophen-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(3-Phenyl-1H-pyrazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-[4-(2-Allylamino-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(4-Imidazol-1-yl-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(3-Methyl-benzo[b]thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(4-Methyl-pent-2-enylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Trifluoromethoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,

6-(4-{2-[(2-Piperidin-1-yl-thiazol-5-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(4-Cyclohexyl-butylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Cyclohexyl-ethylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Chloro-6-fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Cyclopropylmethyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(Naphthalen-1-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Naphthalen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Quinolin-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(2,6-Dichloro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Indan-1-ylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Hydroxy-5-methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Bromo-4-fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Fluoro-2-trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Chloro-4-fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-[4-(2-Cyclooctylamino-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(2-Phenoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Cyclobutylmethyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Cycloheptylmethyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(2-Morpholin-4-yl-thiazol-5-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(2,4-Dichloro-thiazol-5-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(2-Chloro-thiazol-5-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(Cyclopentylmethyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[(3,5-Dimethyl-isoxazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(5-Methyl-isoxazol-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(3-Phenyl-isoxazol-5-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-[4-(2-{[3-(4-Chloro-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-amino}-ethyl)-phenoxy]-  
nicotinamide,  
6-(4-{2-[(5-p-Tolyl-[1,3,4]oxadiazol-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide,  
6-{4-[2-(1-Phenyl-ethylamino)-ethyl]-phenoxy}-nicotinamide,  
6-[4-(3-Benzylamino-propyl)-phenoxy]-nicotinamide,  
6-{4-[3-(Benzyl-pentyl-amino)-propyl]-phenoxy}-nicotinamide,

6-{4-[3-(Benzyl-phenethyl-amino)-propyl]-phenoxy}-nicotinamide,  
6-(4-{3-[Benzyl-(3-cyclopentyl-propyl)-amino]-propyl}-phenoxy)-nicotinamide,  
6-[4-(3-{Benzyl-[2-(3-fluoro-phenyl)-ethyl]-amino}-propyl)-phenoxy]-nicotinamide,  
6-[4-(3-Pentylamino-propyl)-phenoxy]-nicotinamide,  
6-[4-(3-Phenethylamino-propyl)-phenoxy]-nicotinamide,  
6-{4-[3-(3-Cyclopentyl-propylamino)-propyl]-phenoxy}-nicotinamide,  
6-(4-{3-[2-(3-Fluoro-phenyl)-ethylamino]-propyl}-phenoxy)-nicotinamide,  
(R)-6-[4-(2-Benzylamino-propyl)-phenoxy]-nicotinamide,  
(R)-6-[4-(2-Dibenzylamino-propyl)-phenoxy]-nicotinamide,  
6-[4-(2-Benzylamino-2-methyl-propyl)-phenoxy]-nicotinamide,  
6-[4-(2-Methyl-2-pentylamino-propyl)-phenoxy]-nicotinamide,  
6-[4-(2-Methyl-2-phenethylamino-propyl)-phenoxy]-nicotinamide,  
6-(4-{2-[2-(3-Fluoro-phenyl)-ethylamino]-2-methyl-propyl}-phenoxy)-nicotinamide,  
6-{4-[2-(3-Cyclopentyl-propylamino)-2-methyl-propyl]-phenoxy}-nicotinamide,  
6-[4-(3-Benzylamino-butyl)-phenoxy]-nicotinamide,  
6-[4-(3-Pentylamino-butyl)-phenoxy]-nicotinamide,  
6-[4-(3-Propylamino-butyl)-phenoxy]-nicotinamide,  
6-[4-(3-Methylamino-butyl)-phenoxy]-nicotinamide,  
6-[4-(3-Phenethylamino-butyl)-phenoxy]-nicotinamide,  
6-(4-{3-[2-(3-Fluoro-phenyl)-ethylamino]-butyl}-phenoxy)-nicotinamide,  
6-(4-{3-[2-(3-Chloro-phenyl)-ethylamino]-butyl}-phenoxy)-nicotinamide,  
6-(4-{3-[(Furan-2-ylmethyl)-amino]-butyl}-phenoxy)-nicotinamide,  
6-{4-[3-(2-Thiophen-2-yl-ethylamino)-butyl]-phenoxy}-nicotinamide,  
6-{4-[3-(Cyclopropylmethyl-amino)-butyl]-phenoxy}-nicotinamide,  
6-{4-[3-(3-Trifluoromethyl-benzylamino)-butyl]-phenoxy}-nicotinamide,  
6-{4-[3-(4-Fluoro-benzylamino)-butyl]-phenoxy}-nicotinamide,  
6-{4-[3-(3-Fluoro-benzylamino)-butyl]-phenoxy}-nicotinamide,  
6-[4-(3-Allylamino-butyl)-phenoxy]-nicotinamide,  
6-{4-[3-(4-Chloro-benzylamino)-butyl]-phenoxy}-nicotinamide,  
6-{4-[3-(4-Methoxy-benzylamino)-butyl]-phenoxy}-nicotinamide,  
6-{4-[3-(4-Trifluoromethyl-benzylamino)-butyl]-phenoxy}-nicotinamide,  
6-{4-[3-(4-Trifluoromethoxy-benzylamino)-butyl]-phenoxy}-nicotinamide,

6-{4-[3-(3-Trifluoromethoxy-benzylamino)-butyl]-phenoxy}-nicotinamide,  
(1R)-6-{4-[3-(1-Phenyl-ethylamino)-butyl]-phenoxy}-nicotinamide,  
(1S)-6-{4-[3-(1-Phenyl-ethylamino)-butyl]-phenoxy}-nicotinamide,  
6-[4-(2-Benzylamino-propyl)-phenoxy]-nicotinamide,  
6-[4-(2-Pentylamino-propyl)-phenoxy]-nicotinamide,  
6-[4-(2-Propylamino-propyl)-phenoxy]-nicotinamide,  
6-[4-(2-Methylamino-propyl)-phenoxy]-nicotinamide,  
6-[4-(2-Phenethylamino-propyl)-phenoxy]-nicotinamide,  
6-(4-{2-[2-(3-Fluoro-phenyl)-ethylamino]-propyl}-phenoxy)-nicotinamide,  
6-(4-{2-[2-(3-Chloro-phenyl)-ethylamino]-propyl}-phenoxy)-nicotinamide,  
6-(4-{2-[(Furan-2-ylmethyl)-amino]-propyl}-phenoxy)-nicotinamide,  
6-{4-[2-(2-Thiophen-2-yl-ethylamino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Cyclopropylmethyl-amino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Trifluoromethyl-benzylamino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Fluoro-benzylamino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Fluoro-benzylamino)-propyl]-phenoxy}-nicotinamide,  
6-[4-(2-Allylamino-propyl)-phenoxy]-nicotinamide,  
6-{4-[2-(4-Chloro-benzylamino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Trifluoromethyl-benzylamino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Methoxy-benzylamino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Trifluoromethoxy-benzylamino)-propyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Trifluoromethoxy-benzylamino)-propyl]-phenoxy}-nicotinamide,  
(1S)-6-{4-[2-(1-Phenyl-ethylamino)-propyl]-phenoxy}-nicotinamide,  
(1R)-6-{4-[2-(1-Phenyl-ethylamino)-propyl]-phenoxy}-nicotinamide,  
6-[4-(2-Benzylamino-1-methyl-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(Benzyl-pentyl-amino)-1-methyl-ethyl]-phenoxy}-nicotinamide,  
6-[4-(1-Methyl-2-pentylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Benzylamino-1,1-dimethyl-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(Cyclohexylmethyl-amino)-1,1-dimethyl-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(2-Chloro-benzylamino)-1,1-dimethyl-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Fluoro-benzylamino)-1,1-dimethyl-ethyl]-phenoxy}-nicotinamide,  
6-[4-(3-Phenylamino-propyl)-phenoxy]-nicotinamide,

6-[4-(2-Dimethylamino-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-nicotinamide,  
6-[4-(2-Morpholin-1-yl-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Benzoyl-piperidin-1-yl)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3-Methyl-piperidin-1-yl)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(3,5-Dimethyl-piperidin-1-yl)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Benzhydryl-piperidin-1-yl)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(4-Phenyl-piperidin-1-yl)-ethyl]-phenoxy}-nicotinamide,  
6-(4-{2-[3-Fluoro-phenyl]-piperidin-1-yl}-ethyl)-phenoxy)-nicotinamide,  
6-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-nicotinamide,  
6-{4-[2-(Benzyl-methyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Benzyl-ethyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Benzyl-propyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Benzyl-butyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Benzyl-cyclopropylmethylamino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Benzyl-isobutyl-amino)-ethyl]-phenoxy}-nicotinamide,  
6-{4-[2-(Benzyl-(3-methyl-butyl)-amino)-ethyl]-phenoxy}-nicotinamide,  
6-[4-(2-Benzoylamino-ethyl)-phenoxy]-nicotinamide,  
4-[4-(2-Benzylamino-ethyl)-phenoxy]-2-fluoro-benzamide,  
2-[4-(2-Benzylamino-ethyl)-phenoxy]-4-fluoro-benzamide,  
4-[4-(2-Benzylamino-ethyl)-phenoxy]-2-chloro-benzamide,  
6-[4-(2-Benzylamino-ethyl)-2-methyl-phenoxy]-nicotinamide,  
6-[2-Methyl-4-(phenethylamino-methyl)-phenoxy]nicotinamide,  
6-[2-Fluoro-4-(phenethylamino-methyl)-phenoxy]nicotinamide,  
6-[2-Ethoxy-4-(phenethylamino-methyl)-phenoxy]nicotinamide,  
6-[2-Chloro-4-(phenethylamino-methyl)-phenoxy]nicotinamide,

6-[3-Chloro-4-(phenethylamino-methyl)-phenoxy]nicotinamide,  
6-[2-Methyl-4-(3-methyl-butylamino-methyl)-phenoxy]nicotinamide,  
6-[2-Fluoro-4-(3-methyl-butylamino-methyl)-phenoxy]nicotinamide,  
6-[2-Chloro-4-(3-methyl-butylamino-methyl)-phenoxy]nicotinamide,  
6-[2-Ethoxy-4-(3-methyl-butylamino-methyl)-phenoxy]nicotinamide,  
6-{4-[2-Cyclopentyl-ethylamino)-methyl]-2-methyl-phenoxy}-nicotinamide,  
6-{4-[2-Cyclopentyl-ethylamino)-methyl]-2-fluoro-phenoxy}-nicotinamide,  
6-{2-Chloro-4-[2-Cyclopentyl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[2-Cyclopentyl-ethylamino)-methyl]-2-ethoxy-phenoxy}-nicotinamide,  
6-{2-Methyl-4-[2-thiophen-2-yl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-{[2-(3-Fluoro-phenyl)-ethylamino]-methyl}-2-methyl-phenoxy)-nicotinamide,  
6-{2-Methyl-4-[(2-o-tolyl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-methyl-phenoxy}-nicotinamide,  
6-(4-{[2-(3-Chloro-phenyl)-ethylamino]-methyl}-2-methyl-phenoxy)-nicotinamide,  
6-(4-Butylaminomethyl-2-methyl-phenoxy)-nicotinamide,  
6-(2-Methyl-4-{[methyl-(3-methyl-butyl)-amino]-methyl}-phenoxy)-nicotinamide,  
6-{2-Methyl-4-[(methyl-phenethyl-amino)-methyl]-phenoxy}-nicotinamide,  
3-Fluoro-4-[4-(phenethylamino-methyl)-phenoxy]-benzamide,  
3-Chloro-4-[4-(phenethylamino-methyl)-phenoxy]-benzamide,  
2-Chloro-4-[4-(phenethylamino-methyl)-phenoxy]-benzamide,  
3-Fluoro-4-{2-methyl-4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide,  
4-(4-Benzylamino-phenoxy)-benzamide,  
4-(4-Phenethylamino-phenoxy)-benzamide,  
6-[4-(Benzylamino-methyl)-phenoxy]-nicotinamide,  
6-(4-Allylaminomethyl-phenoxy)-nicotinamide,  
6-{4-[(4-Methoxy-benzylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(3-Trifluoromethyl-benzylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2-Thiophen-2-yl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(3-Fluoro-benzylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-{[(Furan-2-yl)methyl]-amino]-methyl}-phenoxy)-nicotinamide,  
6-(4-{[2-(3-Fluoro-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,



6-{4-[(4-Trifluoromethoxy-benzylamino)-methyl]-phenoxy}-nicotinamide,  
6-[4-(Phenethylamino-methyl)-phenoxy]-nicotinamide,  
6-(4-{[2-(3-Chloro-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-(4-{[2-(4-Sulfamoyl-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-{4-[(3-Phenyl-propylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(3,3-Diphenyl-propylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(3,3-Dimethyl-butylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-{[2-(2-Methoxy-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-{4-[(2-Phenylamino-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2-Phenyl-propylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2-Pyridin-2-yl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-{[2-(2-Chloro-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-{4-[(2-Pyridin-3-yl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2,2-Diphenyl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2-Cyclohexyl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2-Methylsulfanyl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(6-Hydroxy-hexylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2-Dimethylamino-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-Decylaminomethyl-phenoxy)-nicotinamide,  
6-{4-[(2-Ethyl-hexylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-{[(Tetrahydro-furan-2-ylmethyl)-amino]-methyl}-phenoxy)-nicotinamide,  
6-{4-[(2-Pyrrolidin-1-yl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-{[2-(1-Methyl-pyrrolidin-2-yl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-(4-{[2-(1H-Imidazol-4-yl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-(4-{[3-(2-Methyl-piperidin-1-yl)-propylamino]-methyl}-phenoxy)-nicotinamide,  
6-{4-[(2-Diisopropylamino-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-{4-[(2-Cyclohex-1-enyl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-Pentylaminomethyl-phenoxy)-nicotinamide,  
4-{4-[(4-Trifluoromethoxy-benzylamino)-methyl]-phenoxy}-benzamide,  
4-(4-{[2-(3-Chloro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-{4-[(4-Trifluoromethyl-benzylamino)-methyl]-phenoxy}-benzamide,

4-{4-[(4-Fluoro-benzylamino)-methyl]-phenoxy}-benzamide,  
4-(4-Pentylaminomethyl-phenoxy)-benzamide,  
4-{4-[(2-Phenyl-propylamino)-methyl]-phenoxy}-benzamide,  
4-(4-{[2-(2-Chloro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-(4-{[2-(2,4-Dichloro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-(4-{[2-(4-Fluoro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-(4-{[2-(3-Fluoro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-(4-{[2-(2-Fluoro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-(4-{[2-(2,5-Dimethoxy-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-(4-{[2-(2,6-Dichloro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
4-{4-[(2-o-Tolyl-ethylamino)-methyl]-phenoxy}-benzamide,  
4-{4-[(2,2-Diphenyl-ethylamino)-methyl]-phenoxy}-benzamide,  
4-[4-(3-Phenyl-propylamino)-phenoxy]-benzamide,  
4-{4-[(2-Cyclopentyl-ethylamino)-methyl]-phenoxy}-benzamide,  
4-{4-[(2,6-Dichloro-benzylamino)-methyl]-phenoxy}-benzamide,  
4-(4-{[(Furan-2-ylmethyl)-amino]-methyl}-phenoxy)-benzamide,  
6-(4-{[2-(3,4-Dichloro-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-(4-{[2-(2-Ethoxy-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-{4-[(2-o-Tolyl-ethylamino)-methyl]-phenoxy}-nicotinamide,  
6-(4-{[2-(2-Phenoxy-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
6-[4-((2-Thiophenyl-ethylamino)-methyl)-2-ethoxy phenoxy] nicotinamide,  
6-[4-((3-Methyl-butylamino)-methyl)-2-ethoxy phenoxy] nicotinamide methanesulfonate salt,  
6-[4-((3-Dimethyl-butylamino)-methyl)-2-ethoxy phenoxy] nicotinamide,  
6-[4-(Butylamino-methyl)-2-ethoxy phenoxy] nicotinamide,  
6-[4-((2-Phenyl-ethylamino)-methyl)-2,5-dimethyl phenoxy] nicotinamide,  
6-[4-((2-Cyclopentyl-ethylamino)-methyl)-2-ethoxy phenoxy] nicotinamide metanosulfonate salt,  
6-[4-((3-Methyl-butylamino)-methyl)-2,5-dimethyl phenoxy] nicotinamide  
6-(4-Iodo-phenoxy)-nicotinamide,  
(±)-6-(4-Piperidin-3-yl-phenoxy)-nicotinamide,  
(±)-6-[4-(1-Benzyl-piperidin-3-yl)-phenoxy]-nicotinamide,

(±)-6-[4-(1-Cyclohexylmethyl-piperidin-3-yl)-phenoxy]-nicotinamide,  
(±)-6-[4-(1-Methyl-piperidin-3-yl)-phenoxy]-nicotinamide,  
(±)-6-[4-(1-(3-Fluoro-benzyl)-piperidin-3-yl)-phenoxy]-nicotinamide,  
(±)-6-[4-(1-(2-Fluoro-benzyl)-piperidin-3-yl)-phenoxy]-nicotinamide,  
(±)-6-[4-(1-Hexyl-piperidin-3-yl)-phenoxy]-nicotinamide,  
(±)-6-{4-[1-(3-Methyl-butyl)-piperidin-3-yl]-phenoxy}-nicotinamide,  
(±)-6-[4-(1-Phenethyl-piperidin-3-yl)-phenoxy]-nicotinamide,  
(±)-6-{4-[1-(2-Cyclohexyl-ethyl)-piperidin-3-yl]-phenoxy}-nicotinamide,  
6-[4-(4-Benzyl-piperazin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(4-Phenethyl-piperazin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(4-Cyclopentyl-piperazin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-{4-[4-(1-Phenyl-ethyl)-piperazin-1-ylmethyl]-phenoxy}-nicotinamide,  
6-[4-(4-Benzhydryl-piperazin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-{4-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-phenoxy}-nicotinamide,  
6-[4-(4-Phenyl-piperazin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(4-Cyclohexyl-piperazin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(4-Isopropyl-piperazin-1-ylmethyl)-phenoxy]-nicotinamide,  
(3R)-6-{4-[(1-Benzyl-pyrrolidin-3-ylamino)-methyl]-phenoxy}-nicotinamide,  
(3S)-6-{4-[(1-Benzyl-pyrrolidin-3-ylamino)-methyl]-phenoxy}-nicotinamide,  
(±)-6-[4-(2-Phenyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(2-Phenyl-pyrrolidin-1-ylmethyl)-phenoxy]-nicotinamide, hydrochloric acid salt,  
(±)-6-[4-(3-Phenyl-pyrrolidin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(4-Phenyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(3-Phenyl-azepan-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(4-Phenyl-azepan-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(4,4-Diphenyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(3,3-Diphenyl-pyrrolidin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-[4-(2,2-Diphenyl-pyrrolidin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-(4-Piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(1,2,4,4a,9,9a-Hexahydro-3-aza-fluoren-3-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-{4-[3-(2-Chloro-phenyl)-piperidin-1-ylmethyl]-phenoxy}-nicotinamide,

(±)-6-{4-[3-(3-Chloro-phenyl)-piperidin-1-ylmethyl]-phenoxy}-nicotinamide,  
(±)-6-{4-[3-(3-Trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-phenoxy}-nicotinamide,  
(±)-6-[4-(3-Methyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(3-Phenethyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(3-Phenpropyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(3-Benzyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[4-(3-Phenyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-{4-[3-(4-Fluoro-phenyl)-piperidin-1-ylmethyl]-phenoxy}-nicotinamide,  
hydrochloric acid salt,  
(±)-6-{4-[3-(2-Fluoro-phenyl)-piperidin-1-ylmethyl]-phenoxy}-nicotinamide,  
hydrochloric acid salt,  
(±)-6-[4-(3-Cyclohexyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide, hydrochloric acid salt,  
(±)-6-[2-Methyl-4-(3-phenyl-piperidin-1-ylmethyl)-phenoxy]-nicotinamide, hydrochloric acid salt,  
(±)-6-[2-Methyl-4-(3-phenyl-azepan-1-ylmethyl)-phenoxy]-nicotinamide, hydrochloric acid salt,  
(±)-6-[2-Methyl-4-(4-phenyl-azepan-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-1-{6-[2-Methyl-4-(3-phenyl-pyrrolidin-1-ylmethyl)-phenoxy]-pyridin-3-yl}-ethanone,  
(±)-5-(1,1-Difluoro-ethyl)-2-[2-methyl-4-(3-phenyl-pyrrolidin-1-ylmethyl)-phenoxy]-pyridine hydrochloric acid salt,  
(±)-6-[2-Fluoro-4-(3-phenyl-pyrrolidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[2-Ethoxy-4-(3-phenyl-pyrrolidin-1-ylmethyl)-phenoxy]-nicotinamide,  
(±)-6-[2-Chloro-4-(3-phenyl-pyrrolidin-1-ylmethyl)-phenoxy]-nicotinamide,  
6-(3-Phenethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)nicotinamide,  
6-(3-Benzyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-nicotinamide,  
6-[4-(Phenethylaminomethyl)phenoxy]nicotinamide,  
{2-[4-(5-Aminomethylpyridin-2-yloxy)phenyl]ethyl}benzylamine,  
5-[4-(Phenethylaminomethyl)phenoxy]pyridine-2-carboxamide,  
2-[4-(2-Benzylaminoethyl)phenoxy]nicotinamide,

6-[4-(2-Benzylaminoethyl)phenoxy]pyridine-2-carboxamide,  
2-[4-(2-Benzylaminoethyl)phenoxy]isonicotinamide,  
N-Methyl-6-[4-(phenethylaminomethyl)phenoxy]nicotinamide,  
5-[4-(Phenethylaminomethyl)phenoxy]pyrazine-2-carboxamide,  
5-(4-{[2-(4-Fluorophenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide,  
5-{4-[(3-Methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide methanesulfonate,  
5-{2-Methyl-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-(4-{[2-(3-Trifluoromethylphenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate,  
5-{4-[(2-Thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-{2-Methyl-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-{2-Methoxy-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-{4-[(2-Cyclopentylethylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-{4-[(2-Cyclopentylethylamino)methyl]-2-methylphenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-{4-[(2-Cyclopentylethylamino)methyl]-2-methoxyphenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-(4-{[(Benzo[b]thiophen-3-ylmethyl)amino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate,  
5-(4-{[2-(4-Methoxyphenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate,  
5-(4-{[2-(3-Fluorophenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate,  
5-(4-{[2-(2-Fluorophenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide  
methanesulfonate,

5-{2-Fluoro-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide  
methanesulfonate,  
5-{2-Methyl-4-[(3-methylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide  
methanesulfonate,  
5-(2-Fluoro-4-pentylaminomethylphenoxy)pyridine-2-carboxamide  
5-{2-Fluoro-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy} pyridine-2-carboxamide,  
5-{2-Fluoro-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy} pyridine-2-carboxamide,  
5-{2-Fluoro-4-[(2-*m*-tolylethylamino)methyl]phenoxy}pyridine-2-carboxamide,  
5-(2-Fluoro-4-{[2-(4-fluorophenyl)ethylamino]methyl}phenoxy)pyridine-2-carboxamide,  
5-{2-Chloro-4-[(3-methylbutylamino)methyl]phenoxy}pyridine-2-carboxamide,  
5-(2-Chloro-4-(pentylaminomethyl)phenoxy)pyridine-2-carboxamide,  
5-{2-Chloro-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide,  
5-{2-Chloro-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide,  
6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}nicotinamide,  
5-(2-Fluoro-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyridine-2-  
carboxamide,  
5-{2-Fluoro-4-[(2-*o*-tolylethylamino)methyl]phenoxy}pyridine-2-carboxamide,  
5-{4-[(2-Naphthalen-2-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide,  
5-{4-[(2-Naphthalen-1-ylethylamino)methyl]phenoxy}pyridine-2-carboxamide,  
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6-{2-Methoxy-4-[(2-thiophen-2-ylethylamino)methyl]phenoxy}nicotinamide,  
6-{2-Methoxy-4-[(2-*o*-tolylethylamino)methyl]phenoxy}nicotinamide,  
6-{2-Methoxy-4-[(2-*m*-tolylethylamino)methyl]phenoxy}nicotinamide,  
6-{4-[(3,3-Dimethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide,  
6-{2-Methoxy-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy}nicotinamide,  
6-(4-Butylaminomethyl-2-methoxyphenoxy)nicotinamide,  
6-(2-Methoxy-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)nicotinamide,  
6-{2-Methoxy-4-[(2-morpholin-4-ylethylamino)methyl]phenoxy}nicotinamide,  
6-{4-[(2-Ethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide,  
6-(4-{[2-(4-Fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)nicotinamide,  
6-(4-{[2-(2-Fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)nicotinamide,

6-(4-Hexylaminomethyl-2-methoxyphenoxy)nicotinamide,  
6-{2-Methoxy-4-[(4-methylpentylamino)methyl]phenoxy}nicotinamide  
methanesulfonate,  
6-{2-Methoxy-4-[(2-*p*-tolylethylamino)methyl]phenoxy}nicotinamide methanesulfonate,  
5-(2-Methyl-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyrazine-2-  
carboxamide,  
5-{4-[(3,3-Dimethylbutylamino)methyl]-2-methylphenoxy}pyrazine-2-carboxamide,  
5-{4-[(3-Methylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide,  
5-(4-{[2-(Tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)pyrazine-2-carboxamide,  
5-{4-[(3,3-Dimethylbutylamino)methyl]phenoxy}pyrazine-2-carboxamide,  
6-(2-Methoxy-4-{[2-(tetrahydropyran-4-yl)ethylamino]methyl}phenoxy)nicotinamide  
methanesulfonate,  
6-(4-Hexylaminomethyl-2-methoxyphenoxy)nicotinamide methanesulfonate,  
6-(2-Methoxy-4-pentylaminomethylphenoxy)nicotinamide methanesulfonate,  
6-(4-Butylaminomethyl-2-methoxyphenoxy)nicotinamide methanesulfonate,  
6-{2-Methoxy-4-[(2-pyridin-3-ylethylamino)methyl]phenoxy}nicotinamide  
methanesulfonate,  
6-{4-[(2-Ethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide methanesulfonate,  
6-{4-[(3,3-Dimethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide  
methanesulfonate,  
6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}nicotinamide methanesulfonate,  
6-(2-Phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy)nicotinamide,  
6-[2-(3-Methylbutyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide,  
6-[2-(3-Methylpentyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yloxy]nicotinamide,  
(±)-6-{4-[2-(2-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide,  
(±)-(*cis*)-6-{4-[2-(3-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide,  
(±)-(*trans*)-6-{4-[2-(3-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide,  
(±)-6-{4-[2-((*trans*)-4-Hydroxycyclohexylamino)ethyl]phenoxy}nicotinamide,  
(±)-6-{4-[2-((*trans*)-2-Hydroxycyclopentylamino)ethyl]phenoxy}nicotinamide,  
4-[5-(Phenethylamino-methyl)-pyridin-2-yloxy]-benzamide dihydrochloride 4-{5-[(3-  
Trifluoromethyl-benzylamino)-methyl]-pyridin-2-yloxy}-benzamide 4-{5-[(3-Phenyl-  
propylamino)-methyl]-pyridin-2-yloxy}-benzamide

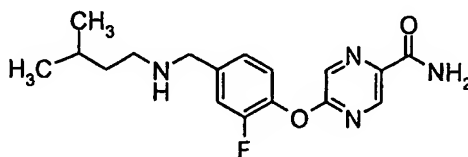
4-{5-[(4-Fluoro-benzylamino)-methyl]-pyridin-2-yloxy}-benzamide 4-[5-(Isobutylamino-methyl)-pyridin-2-yloxy]-benzamide 4-{5-[(2-Thiophen-2-yl-ethylamino)-methyl]-pyridin-2-yloxy}-benzamide  
 4-(5-{[2-(3-Fluoro-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide  
 4-(5-{[2-(2-Methoxy-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide 4-(5-{[2-(2-Chloro-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide 4-[5-(3-Phenyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxy]-benzamide 4-{5-[(3,3-Dimethyl-butylamino)-methyl]-pyridin-2-yloxy}-benzamide 4-{5-[(3-Methyl-butylamino)-methyl]-pyridin-2-yloxy}-benzamide  
 4-{3-Chloro-5-[(2-thiophen-2-yl-ethylamino)-methyl]-pyridin-2-yloxy}-benzamide  
 4-(3-Chloro-5-{[2-(3-chloro-phenyl)-ethylamino]-methyl}-pyridin-2-yloxy)-benzamide  
 and pharmaceutically acceptable salts, solvates, enantiomers, and mixtures of diastereomers thereof.

Also particularly preferred is a compound selected from the group consisting of:

6-[2-Chloro-4-(3-methyl-butylamino-methyl)-phenoxy]nicotinamide,  
 6-(2-Methoxy-4-pentylaminomethylphenoxy)nicotinamide,  
 6-{2-Methoxy-4-[(3-methylbutylamino)methyl]phenoxy}nicotinamide,  
 6-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-methyl-phenoxy}-nicotinamide,  
 6-{4-[(3,3-Dimethylbutylamino)methyl]-2-methoxyphenoxy}nicotinamide,  
 5-(2-Fluoro-4-pentylaminomethylphenoxy)pyridine-2-carboxamide,  
 6-(4-{[2-(2-Fluorophenyl)ethylamino]methyl}-2-methoxyphenoxy)nicotinamide,  
 4-(4-{[2-(4-Fluoro-phenyl)-ethylamino]-methyl}-phenoxy)-benzamide,  
 6-(4-{[2-(3-Fluoro-phenyl)-ethylamino]-methyl}-phenoxy)-nicotinamide,  
 a combination of one or more of the above, and a pharmaceutically acceptable salt, solvate, enantiomer, diastereomer and diastereomeric mixture thereof.

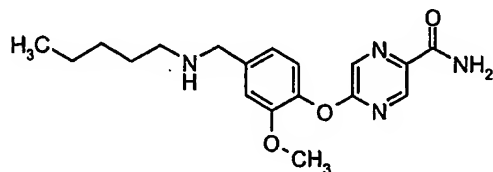
Most preferred is a compound selected from the group consisting of:

5-{2-Fluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-pyrazine-2-carboxamide

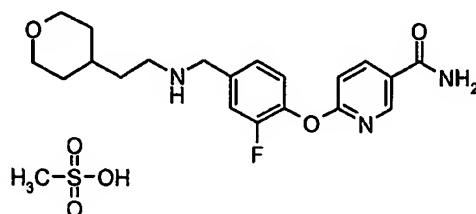




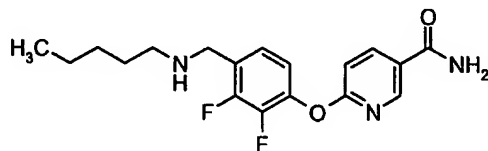
5-(2-Methoxy-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxamide



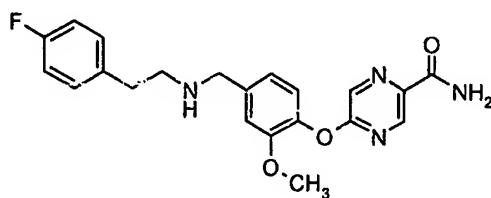
6-(2-Fluoro-4-[[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl]-phenoxy)-nicotinamide;  
methanesulfonic acid salt



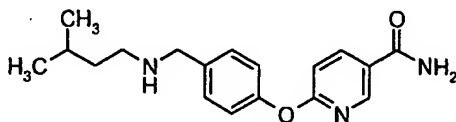
6-(2,3-Difluoro-4-pentylaminomethyl-phenoxy)-nicotinamide



5-(4-[[2-(4-Fluoro-phenyl)-ethylamino]-methyl]-2-methoxy-phenoxy)-pyrazine-2-carboxamide

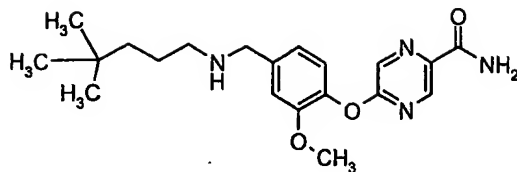


6-{4-[(3-Methyl-butylamino)-methyl]-phenoxy}-nicotinamide

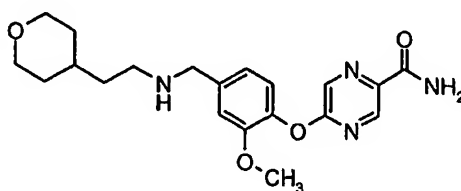


5-{4-[(4,4-Dimethyl-pentylamino)-methyl]-2-methoxy-phenoxy}-pyrazine-2-carboxamide

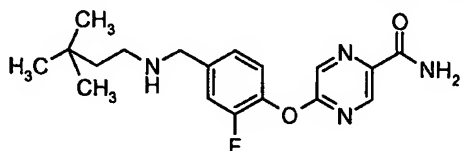
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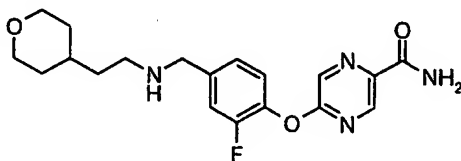
5-(2-Methoxy-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-pyrazine-2-carboxamide



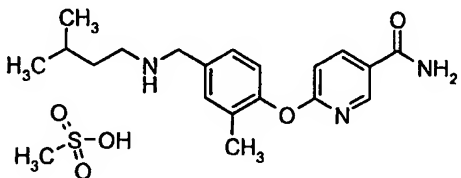
5-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-fluoro-phenoxy}-pyrazine-2-carboxamide



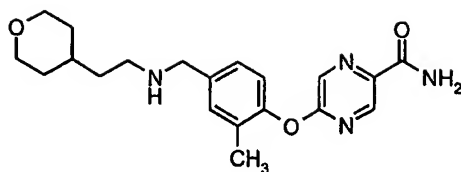
5-(2-Fluoro-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-pyrazine-2-carboxamide



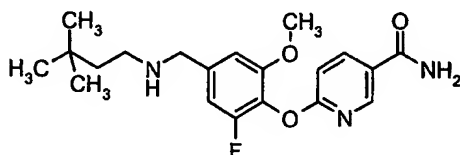
6-{2-Methyl-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide; methanesulfonic acid salt



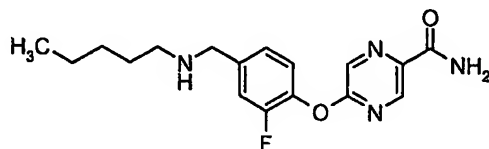
5-(2-Methyl-4-{[2-(tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-pyrazine-2-carboxamide,



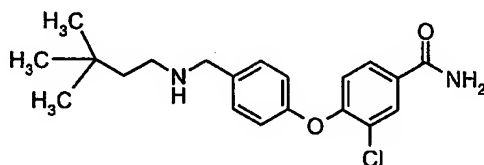
6-{4-[(3,3-Dimethyl-butylamino)-methyl]-2-fluoro-6-methoxy-phenoxy}-nicotinamide,



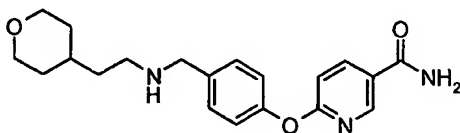
5-(2-Fluoro-4-pentylaminomethyl-phenoxy)-pyrazine-2-carboxamide



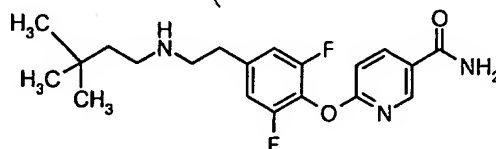
3-Chloro-4-{4-[(3,3-dimethyl-butylamino)-methyl]-phenoxy}-benzamide



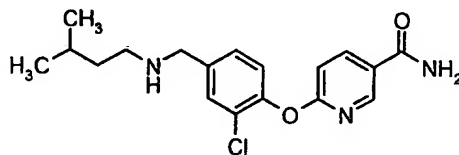
6-(4-{[2-(Tetrahydro-pyran-4-yl)-ethylamino]-methyl}-phenoxy)-nicotinamide



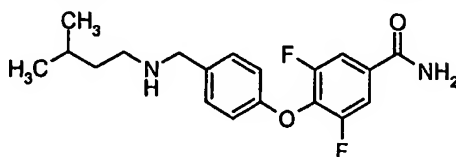
6-{4-[2-(3,3-Dimethyl-butylamino)-ethyl]-2,6-difluoro-phenoxy}-nicotinamide



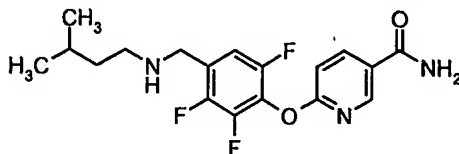
6-{2-Chloro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



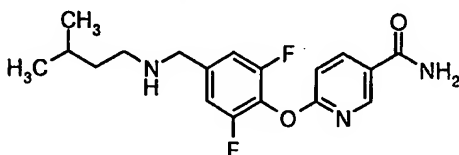
3,5-Difluoro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide



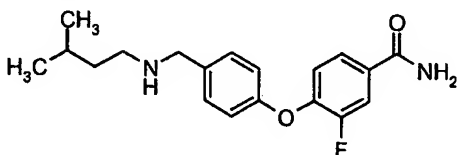
6-{2,3,6-Trifluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



6-{2,6-Difluoro-4-[(3-methyl-butylamino)-methyl]-phenoxy}-nicotinamide



3-Fluoro-4-{4-[(3-methyl-butylamino)-methyl]-phenoxy}-benzamide

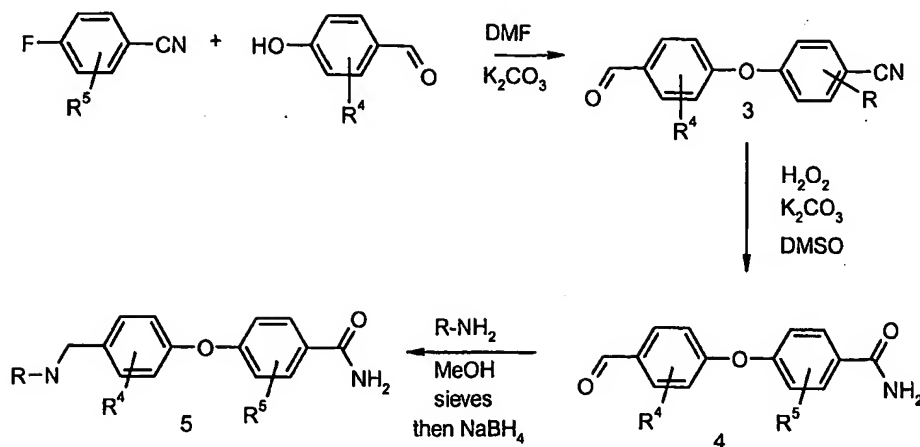


and a pharmaceutically acceptable salt, solvate, enantiomer, diastereomer and diastereomeric mixture thereof.

### Preparing Compounds of the Invention

In a typical protocol, an optionally substituted benzonitrile or pyridine carboxamide or synthon thereof, having a leaving group such as halogen, preferably fluoro, bromo, or chloro, or an alkylsulfonyl or other suitable leaving group is reacted with a nucleophilic group such as for example, hydroxy phenylcarboxaldehyde or synthon or derivative thereof. For example according to Scheme 1,

Scheme 1



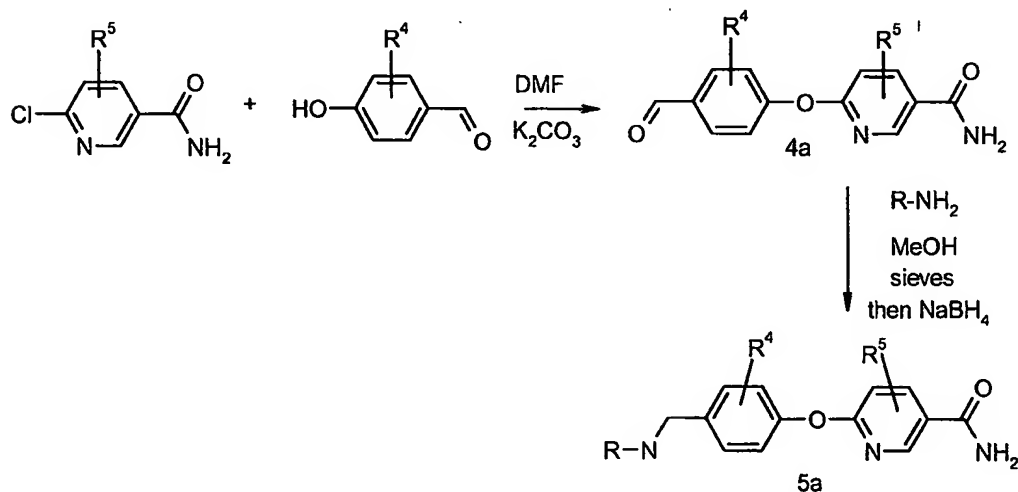
optionally substituted 4-fluorobenzonitrile is reacted with optionally substituted 4-hydroxybenzaldehyde to afford the ether, compound 3, under basic conditions. Basic conditions include the use of bases selected from inorganic and organic bases. Examples of useful inorganic bases include but are not limited to potassium carbonate, sodium hydride, sodium carbonate, sodium hydroxide, potassium hydroxide, calcium carbonate and cesium carbonate. Examples of organic bases include but are not limited to potassium hexamethyl disilazide, n-butyl lithium, Hexamethylphosphorotriamide, (HMPT), and the like. The basic conditions are complemented by the presence of a solvent, preferably an organic solvent. Preferred organic solvents include protic solvents or polar aprotic solvents. Most preferred solvents include dimethylformamide, methanol, dimethylacetamide (DMA), dimethylsulfoxide. A most preferred basic reaction condition involves the use of potassium carbonate in dimethylacetamide at temperatures of about 60 to 100 °C.

The nitrile compound of formula 3 is converted to the carboxamide 4 by hydrolysis procedures known to one of skill in the art. For example, the compound of formula 3 is reacted with potassium carbonate or other suitable base in the presence of hydrogen peroxide in a suitable organic solvent i.e. DMSO or DMF. The resulting amide compound 4 is reductively aminated with a suitably substituted amine. The reductive amination may be performed in two steps or a single step depending on the stability of the intermediate imine. The compound 4 is reacted with a primary or secondary amine (primary amine shown) in methanol as solvent. Molecular sieves may be added to enhance the efficiency of the imine formation. In a second step the reducing agent, typically, sodium borohydride or other hydride reducing agent is added to the reaction

mixture. The progress of the reaction may be monitored by TLC, HPLC, LC-MS or other analytical technique known to one of skill in the art to determine the substantial completion of each step and timing for the addition of the next reagent. The reductive amination of compound 4 results in the compound of formula 5, which is a compound of the invention. Analogues of compounds 3 and 5 having one or more substituent R groups may be prepared by using appropriately substituted starting materials or by inter-conversion of substituent functionality. For example an initial substituent R group may be protected and deprotected appropriately to achieve the desired end substituent R. Alternatively an initial substituent, R may be converted by known 1,2 or 3 step reactions to other desired R substituents.

An alternate protocol illustrated in Scheme 2 shows the use of the carboxamide starting material to prepare, for example, compounds having the pyridinyl B-ring.

Scheme 2

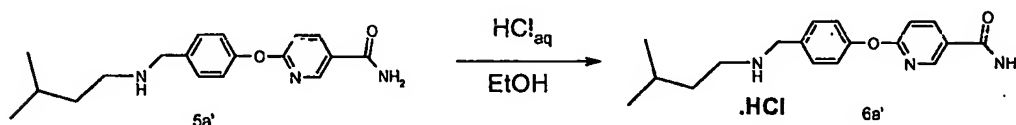


The use of the carboxamide starting material is particularly preferred for compounds of the invention where the B-ring is pyridinyl, pyridazinyl, pyrazinyl or pyrimidinyl group. The carboxamide may be introduced as part of the starting material where the appropriate surrogate for the B-ring is commercially available or may be prepared for certain groups as discussed in the examples. For example, the use of pyridine carboxamide, nicotinamide or substituted analogs thereof, results in substituted derivatives or analogs of compounds of formula 4a or 5a, which are also compounds of

the present invention. Primary and secondary amines are useful for the reductive amination to convert compound (4a) to compound (5a). Examples of useful amines include but are not limited to phenethylamine, 3-methylbutylamine, propylamine, isopropylamine, benzylamine and isopentylamine.

Compounds prepared by this and other schemes disclosed herein or known to one of skill in the art may further be converted to the acid addition salt as shown for example, in Schem 2A.

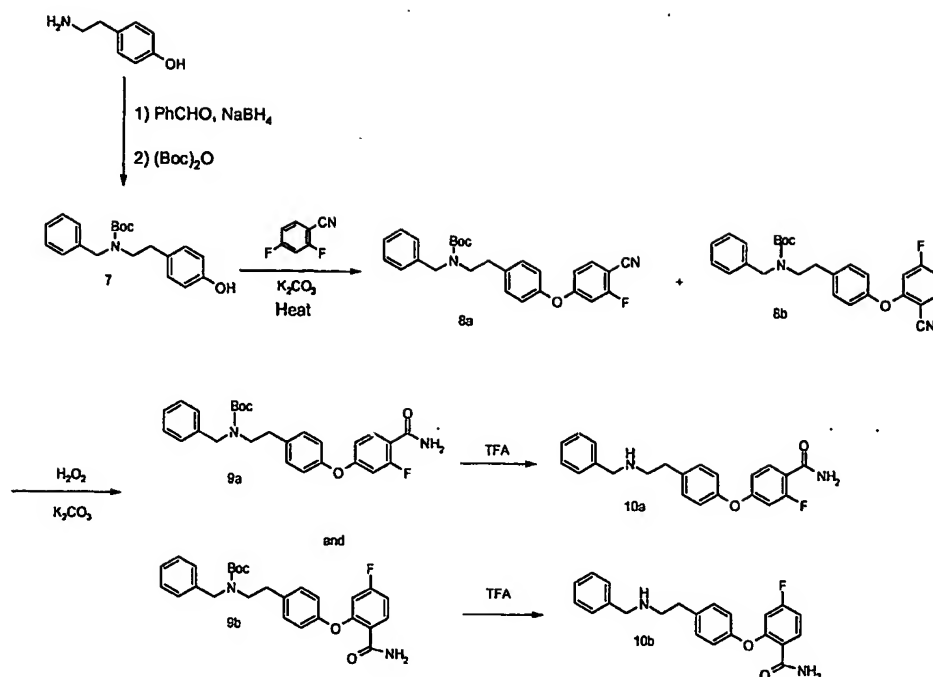
Scheme 2A



Scheme 2A shows preparation of the hydrochloride salt (6a') of compound 5a of Schem 2 wherein RNH<sub>2</sub> is 3-methylbutylamine or other amine group and R<sup>4</sup> and R<sup>5</sup> are both hydrogen. The compound 5a' is dissolved in ethanol and a slight excess (e.g 1.0 to 1.5 mo.ar equivalents) of 1N hydrochloric acid is added at temperatures ranging from about 0 °C to room temperature. The mixture may be allowed to cristasllize over time with or without cooling, or may be evaporated to afford the hydrochloride salt, which may be further purified by trituration with a suitable organic solvent such as toluene, hexanes, diethylether or mixtures thereof. Alternatively, anhydrous HCl may be bubbled into a cold solution of compound 5a' until the reaction is complete or the solution is saturated, and the mixture worked up as appropriate. One of skill in the art is aware of the nuances and the varied techniques for preparing, isolating and purifying acid addition salts, and should achieve comparable results using methods appropriate for the particular substrate without undue experimentation.

A modified protocol for preparing compounds of the invention is provided in Scheme 3 wherein the nucleophilic displacement reaction to form the ether linkage is performed towards the end of the synthesis rather than early on.

Scheme 3



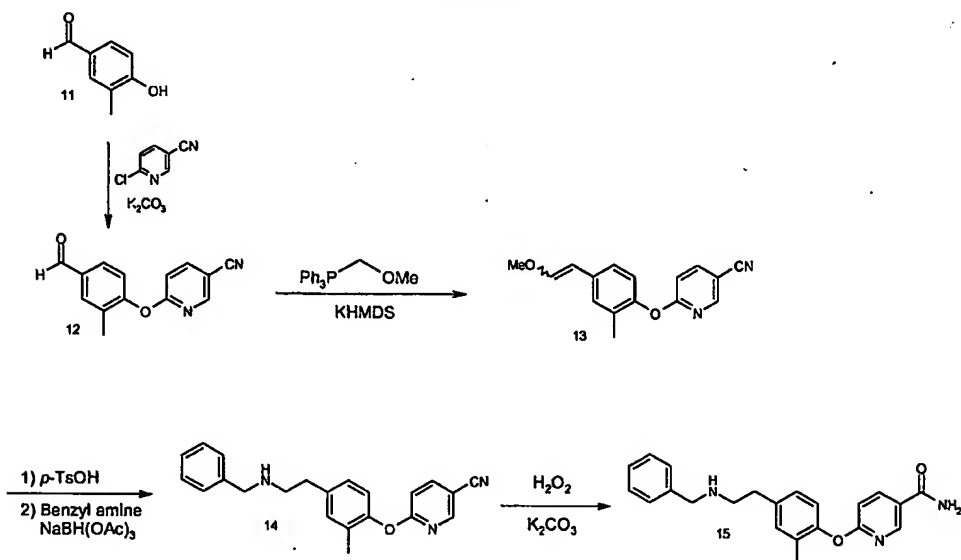
Under this protocol an appropriately substituted aminophenol is reductively aminated with benzaldehyde, which is optionally substituted as appropriate. The reductive amination is accomplished in the presence of sodium borohydride or other reducing agent and a suitable base. Alternatively, and preferably, di-tert-butylidicarbonate (Boc<sub>2</sub>O) is used to afford protection of the incipient free amine as the Boc-protected amine. The resulting phenoxy compound 7 is then reacted with a B ring source such as, for example, phenyl or pyridine carboxamide, benzonitrile or pyridino-nitrile or synthon thereof. The coupling of the B and A-ring sources is performed under basic conditions to afford the ether 8a and 8b for the above example. The coupled product where it exists as a mixture of isomers as in 8a and 8b, the isomers may be separated or used directly in the next step. In the next step, the nitrile group if present as in the current example is hydrolyzed to the carboxamide as discussed previously. The protecting group may be removed by use of hydrochloric acid or trifluoroacetic acid using procedures known to one of skill in the art. One of skill in the art is aware that appropriately substituted analogs of the compound of formula 10a or 10b may be prepared by starting with



appropriately substituted starting materials or surrogates thereof which may be converted to the desired substituents.

Compounds of formula I having varying alkyl chain lengths on the amino side chain may be prepared in one instance by carbonyl elongation reactions. An example is a modified Wittig type reaction as shown in Scheme 4.

Scheme 4

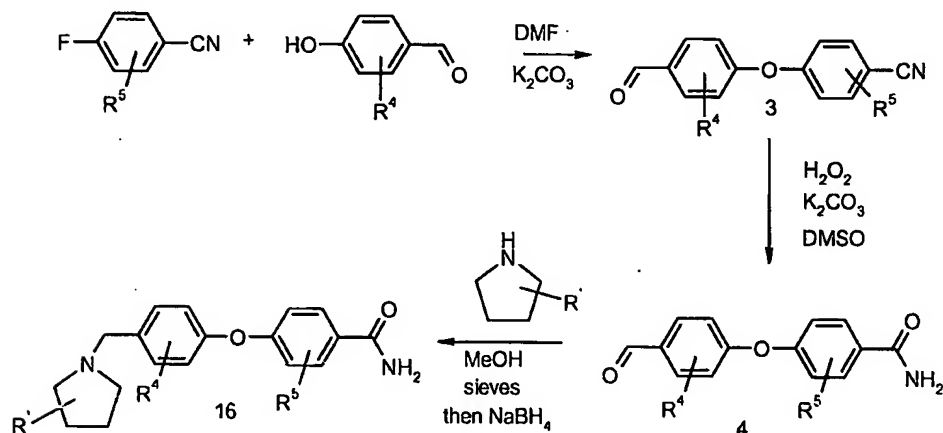


The protocol of Scheme 4 and known variations thereof allow manipulation of the amino side chain for chain length and /or substituents. Under this protocol, optionally substituted 4-hydroxy benzaldehyde i.e. compound 11 is reacted with optionally substituted benzonitrile having a suitable leaving group, e.g. halo, alkylsulfonyl, etc. The nicotinonitrile 12 or analog thereof, is then subjected to a carbonyl elongation reaction such as, for example, the Wittig reaction and variations thereof. (see *Organophosphorus Agents in Organic Synthesis*, J. I. G. Cadogan, Ed., Academic Press London (1979); see also, J. March, *Advanced Organic Chemistry*, 3<sup>rd</sup> Edition, Wiley Interscience, New York New York, (1995). In the example given, the aldehyde 12 is reacted with methoxymethyl triphenylphosphine (available from Aldrich chemical Company, Milwaukee, USA) using a strong base such as, for example, n-butyl lithium, sec-butyl lithium and the like, to generate the incipient carbanion. The resulting vinyethyl ether 13 is hydrolyzed using a strong acid such as, p-toluenesulfonic acid, HCl or sulfuric acid to generate the new

aldehyde. The aldehyde is then reacted with a suitable amine followed by reduction to afford the reductive amination product **14**. Details of each step in the schemes disclosed herein are provided in the experimental section, or may be found in reference organic synthesis texts or are known to one of skill in the art. Some reactions such as the formation of the ylide specie for the Wittig and related reactions perform better at reduced temperatures ranging from about  $-10^{\circ}\text{C}$  to about  $-70^{\circ}\text{C}$ . Other reactions perform better at elevated temperatures ranging from about  $30^{\circ}\text{C}$  to about  $150^{\circ}\text{C}$ , and yet other reactions perform better at ambient temperature ranging from about  $15^{\circ}\text{C}$  to about  $30^{\circ}\text{C}$ .

Compounds of the invention wherein the groups  $\text{R}^1$  and  $\text{R}^2$  combine with each other and with the nitrogen atom to form a nitrogen containing heterocycle may be prepared, for example, according to scheme 5.

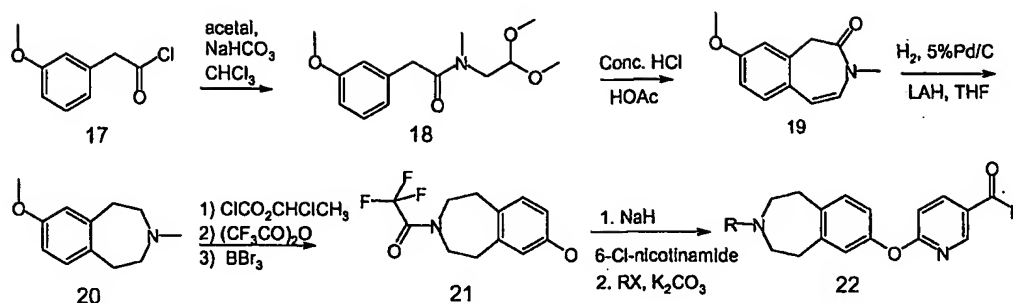
Scheme 5



According to Scheme 5, the reductive amination of aldehyde with amine is performed using a cyclic amine having the desired ring size and /or substituents. For example, the reaction of compound optionally substituted cyclic amine such as for example, optionally substituted pyrrolidine (as shown) with the aldehyde **4** results in the formation of compound **16** having the  $\text{R}^1$  and  $\text{R}^2$  combine together to form the nitrogen containing heterocyclic amine.

Compounds of formula I wherein  $\text{R}^1$  or  $\text{R}^2$  combines with the A ring to form a nitrogen containing heterocycle may be prepared as shown in the following scheme 6.

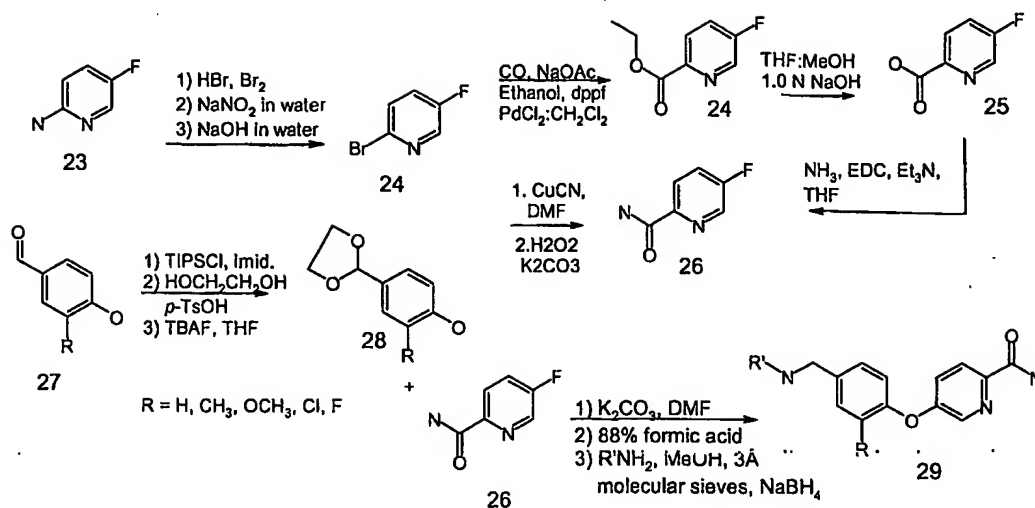
Scheme 6



The scheme above, shows the preparation of the benzo[d]azepine ring as a representative example. As shown the reaction of 3-methoxyphenacetyl chloride (17) with methylamino acetaldehyde dimethylacetal results in the formation of compound 18. Compound (18) is cyclized to the azepin-2-one compound 19. Compound 19 is reduced to the tetrahydrobenzo[d]azepin-2-one compound using, for example, lithium aluminum hydride in THF or 5% palladium on carbon in ethyl acetate. The compound is further deoxygenated and reduced to the tetrahydrobenzo[d]azepine compound 20. Compound 20 is first protected as the trifluoroacetamide, de-methylated with boron tribromide in a suitable polar aprotic solvent, and then reacted with 6-chloronicotinamide, for example, to form the corresponding ether product. The trifluoroacetamide protecting group is removed by basic hydrolysis, i.e. ammonia in methanol, and substitution on the azepine nitrogen results in compounds of the invention 22. Such substitutions may be effected by using a base such as sodium or potassium carbonate in the presence of the electrophile i.e. alkyl, benzyl or aryl halide. Detailed procedures for the practice of the above protocol, as with other protocols described above may be found in the experimental section. Also details for individual steps of protocols disclosed herein may be found in the literature or are known to one of skill in the art.

Compounds of formula I wherein the B-ring is a positional isomer of pyridine may be prepared as shown for example in Scheme 7.

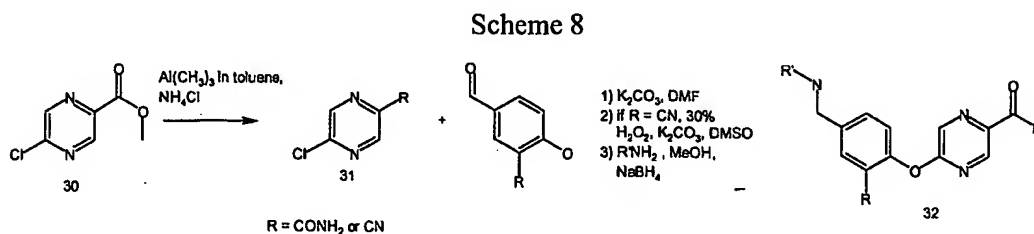
Scheme 7



As shown above, diazotization followed by bromination of 2-amino-5-fluoropyridine (23) affords the 2-bromo-5-fluoropyridine compound 24. The 2-bromo-5-fluoropyridine compound is converted to the ethoxycarbonyl derivative via a hydroxycarbonylation reaction followed by esterification of the incipient carboxylic group. The palladium catalyzed hydroxycarbonylation reaction is known to one of skill in the art and is also disclosed in general organic chemistry reference text. For a variant of the hydroxycarbonylation reaction using the triflate leaving group see Sandro Sacchi and Alessandro Lupi, *Palladium Catalyzed Hydroxycarbonylation of Vinyl and Aryl Triflates: Synthesis of  $\alpha$ ,  $\beta$ -Unsaturated and Aromatic Carboxylic Acids*, *Tetrahedron Letters*, Vol. 33, No. 27, pp. 3939-3942, (1992). The resulting ester may be hydrolyzed to the acid, which is then converted to the carboxamide via a coupling reaction facilitated by a coupling agent such as EDCI for example. Alternatively the 2-bromo-5-fluoropyridine compound may be converted to the nitrile by reaction with copper cyanide in a polar aprotic solvent such as DMF. The nitrile is then hydrolyzed as discussed previously to afford the corresponding carboxamide 26. One of skill in the art is aware that palladium catalyzed cyanation reactions using copper cyanide, palladium source and ligand are available to effect the cyanation reaction discussed above with similar or possibly improved yields. The carboxamide compound 26 is reacted with a substituted or unsubstituted 4-hydroxybenzaldehyde protected as the acetal 28. The resulting etherification product is then reductively aminated with an amine in the presence of

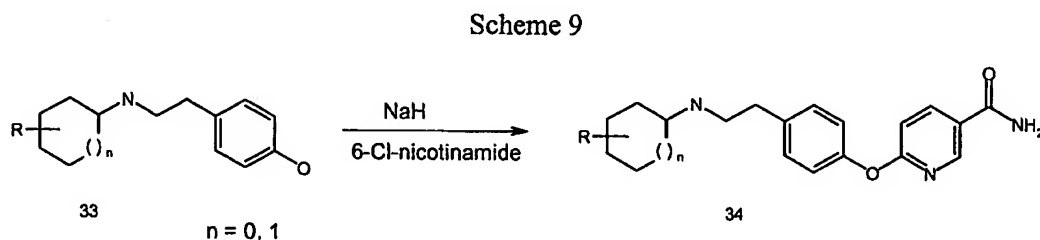
sodium borohydride or other suitable reducing agent to afford the compound of the invention 29 as shown.

Compounds of formula I wherein the B ring is pyrazinyl may be prepared, for example, according to scheme (8) below:



Compounds wherein R<sup>1</sup> and/or R<sup>2</sup> is independently a cyclic group, i.e. saturated or unsaturated monocyclic carbocycle may be prepared as shown below in Scheme 9.

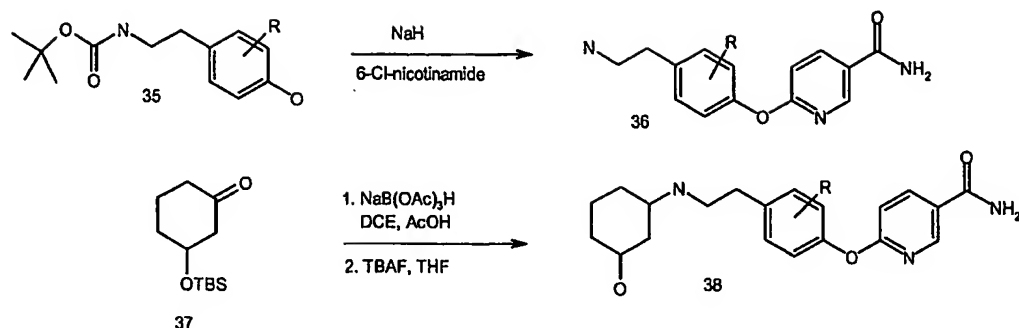
Scheme 9 is affected by reacting the amine 33 incorporating the A-ring, with a halogeno-nicotinamide e.g., 6-chloronicotinamide or a halogeno-nicotinonitrile to form the compound of the invention 34.



Where a halogeno-nicotinonitrile is used, the hydrolysis of the resulting nitrile to form the amide derivative has been disclosed previously. The amine 33 is itself prepared by reductive amination of 4-hydroxy phenacetaldehyde and the respective amine. The phenacetaldehyde may itself be purchased or prepared from the corresponding benzaldehyde by carbonyl elongation reactions i.e. by the Wittig or modified Wittig reaction as discussed previously.

An alternative protocol is shown in Scheme 10.

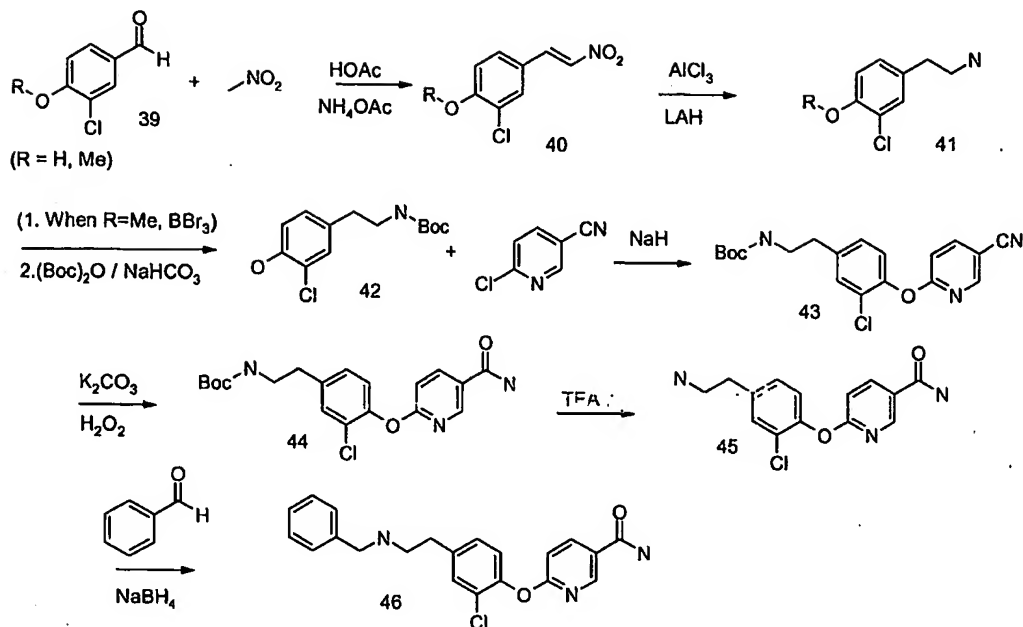
Scheme 10



As shown in Scheme 10, an amine substrate having the A-ring, i.e., 4-hydroxyphenethyl amine is protected at the amine using, for example, the Boc-protecting group or other typical amino protecting groups. The Boc-protected amine 35 is coupled to the B-ring component, i.e., 6-chloronicotinamide (shown) or nicotinonitrile or benzonitrile or analog or derivative thereof. The coupled product is then de-protected and reductively aminated with a cyclic ketone having the desired R<sup>1</sup> and/or R<sup>2</sup> group per the structure and scope of formula I. For the example shown, tertiary butyl dimethyl silyl (TBDMS) protected 3-hydroxycyclohexanone 37 is reacted with the amine 36 having the A and B rings already in place, to form the desired compound of the invention 38 upon desilylation.

The preferred reaction conditions for each step of the reactions or schemes disclosed herein are provided in the experimental section, or known to one of skill in the art, or suggested in the literature or ascertainable with minimal routine experimentation by one of skill in the art following some or all the teachings disclosed and/or referenced herein. Substituents such as "R" and "R'" groups used in the schemes are for illustration purposes only and are not intended to limit the scope of the number and/or type of substituents. One of skill in the art is aware of substituent-types and multiplicities thereof that are suitable and/or possible for a particular position. In general, while a particular substrate or compound is used for illustration purposes, no limitation is implied the workability of the particular scheme for other compounds within the ambit of the invention unless so stated. One of skill in the art is aware that compounds of formula II may also be prepared by the schemes above and by procedures disclosed in the experimental section.

Scheme 11



Certain compounds of the invention may also be accessed by protocols such as Scheme 11. For example, compounds of formula I or II having "y" groups other than hydrogen may be more readily accessed by a Michael addition of nitromethane on an aldehyde e.g., aldehyde 39, having the desired A ring substituents. The resulting product is reduced to afford the saturated amine. When r is methyl the product 41 is deprotected by reaction with  $\text{BBr}_3$ , following procedures disclosed herein and/or known to one of skill in the art. The resulting hydroxyamine is optionally protected for example by use of a Boc- group to afford the compound 42. The protected amino compound 42 is then reacted with appropriately substituted benzamide or nicotinonitrile or nicotinamide to afford a compound of formula I or II after further processing as described previously.

### Method of Using the Invention

As noted above, the compounds of the present invention are useful in blocking the effect of agonists at mu, kappa, and/or delta opioid receptors. As such, the present invention also provides a method for blocking a mu, kappa, delta receptor or receptor combination (heterodimer) thereof in a mammal comprising administering to said mammal a receptor blocking dose of a compound of formula I or II.

The term "receptor blocking dose", as used herein, means an amount of a compound of formula I or II necessary to block a mu, kappa, or delta receptor or receptor combination (heterodimer) thereof following administration to a mammal requiring blocking of a mu, kappa, or delta receptor or receptor combination (heterodimer) thereof.

The compounds of formula I or II or combinations thereof, are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.05 to about 250 mg/kg of body weight. In the treatment of adult humans, the range of about 0.5 to about 100 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician in light of the relevant circumstances, including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration. Therefore, the above dosage ranges are not intended to limit the scope of the invention in any way. The compounds may be administered by a variety of routes such as the oral, transdermal, subcutaneous, intranasal, intramuscular and intravenous routes.

A variety of physiologic functions have been shown to be subject to or influenced by mu, kappa, or delta receptors or receptor combination (heterodimers) in the brain. As such, the compounds of the present invention are believed to have the ability to treat disorders associated with these receptors or combinations thereof, such as eating disorders, opioid overdose, depression, smoking, alcoholism, sexual dysfunction, shock, stroke, spinal damage and head trauma. As such, the present invention also provides methods of treating the above disorders by blocking the effect of agonists at a mu, kappa, delta receptors or receptor combinations (heterodimer) thereof. The compounds of the present invention have been found to display excellent activity in an opioid receptor binding assay which measures the ability of the compounds to block the mu, kappa, delta or receptor combination (heterodimer) thereof.

#### **GTP- $\gamma$ -S Binding Assay**

An SPA - based GTP- $\gamma$ -S assay format was developed based on previous opioid (Emmerson et al., J. Pharm Exp Ther 278,1121,1996; Horng et al., Society for Neuroscience Abstracts, 434.6, 2000) and muscarinic (DeLapp et al., JPET 289, 946,



1999) assay formats. Membranes were re-suspended in 20 mM HEPES, 100 mM NaCl, 5 mM MgCl<sub>2</sub>, 1 mM DTT, and 1 mM EDTA. Fifty (50) mL of GTP- $\gamma$ -[35S], compound, membrane suspension (20 microgram/well), and wheat germ agglutinin coated SPA beads (1mg/well) were added to clear bottom 96 well assay plates. GDP (200 mM) was added to the membrane solution prior to addition to the assay plates. Plates were sealed and incubated for four hours at room temperature then placed in a refrigerator overnight to allow the beads to settle. Signal stability at 4 °C was determined to be > 60 hours. Plates were warmed to room temperature and counted in a Wallac Microbeta scintillation counter. For antagonist assays, specific agonists were added at the following concentrations: (MOR) DAMGO 1 micromolar, (DOR) DPDPE 30 nM, (KOR) U69593 300 nM. Kb's were determined by Cheng-Prusoff equation (see Cheng and Prusoff, Biochem. Pharmacol. 22, 3099, 1973). Results obtained for a representative sample of compounds of the invention in the GTP- $\gamma$ -S Binding Assay are shown in table 1 below.

Table 1

<u>In Vitro</u>			
<u>Antagonism GTP-</u>			
<u><math>\gamma</math>-S</u>			
<u>Compound #</u>	<u>Mu (nM)</u>	<u>Kb (nM)</u>	<u>Delta (nM)</u>
		<u>Kappa</u>	
475	0.843	7.859	17.489
476	0.281	3.378	8.900
478	0.410	4.498	5.779
271	0.200	0.400	4.400
479	0.503	6.855	30.101
252	0.177	2.166	14.121
253	0.068	0.355	0.708
256	0.072	0.894	0.677

#### Ex-Vivo Receptor Binding

In order to bridge in vitro binding affinity and antagonist potency to in vivo potency and efficacy applicants have developed an ex vivo receptor binding assay in rat brain. This assay measures the difference in association (binding) of a high affinity

nonselective opioid receptor radioligand (3H-diprenorphine) in brain tissue isolated from animals receiving vehicle versus compound treatment (less binding of 3H-diprenorphine = greater compound association with opioid receptors). Studies using the ex-vivo receptor binding assay have demonstrated a positive correlation between activity (potency and duration of activity) which also correlates to 24 hour efficacy in dietary induced obese rats.

**Methods.** An opioid receptor ex vivo binding assay measures 3H-diprenorphine binding (0.1 –0.4 nM affinity radioligand for mu, delta and kappa receptors) in rat striatum/nucleus accumbens; a region of the brain that contains a high density of mu, delta and kappa receptors, following oral administration of compounds. Experimentally, a screening dose of 7 mg/kg, p.o. of compound or vehicle is administered to rats. Six hours following compound administration, the animals are sacrificed and the striatum/nucleus accumbens is isolated and homogenized in 10 volumes (weight/volume) binding buffer. The homogenate is then used in a homogenate binding assay using a saturating concentration of 3H-diprenorphine for 30 minutes. The homogenization and assay is performed at 4 °C, to minimize compound redistribution in the in vitro binding portion of the assay. Results are reported (Table 2) as % inhibition of diprenorphine binding, based on the difference in specific binding between compound treated animals versus control animals treated with vehicle alone.

Table 2

Compound of Example No.	Ex Vivo Binding [3H]-Diprenorphine % Inhibition of at 6 hours
	7 mg/kg of test compound
228	> 65%
309	> 60 %
271	> 40%
253	> 40%
481	83%

229	77%
420	75%
447	62%
263	62%
238	59%
446	55%
227	55%
405	55%
431	54%
294	50%
256	40%
272	79%
246	58%
240	38%
LY255582	>40%
Naltrexone®	<40%

#### Acute Feeding Assay (Rat Obesity Assay)

The efficacy of compounds of the present invention has been further verified by the results of a Rat Obesity assay shown in Table 3. The assay results show that compounds of the present invention achieve inhibition of opioid receptors at a level comparable to or superior to that achieved with a previous clinical candidate compound LY255582 disclosed and claimed in U.S. patent 4,891,379.

Table 3

Compound of Example No.	Doses in ug/kg to achieve effective inhibition
290	3
227	0.3
228	0.3
271	0.3
263	≤3
309	≤3

253	$\leq 3$
LY255582	1
Naltrexone®	>10

### Indirect Calorimetry Assay

Twenty-four-hour energy expenditure (EE) and respiratory quotient (RQ) were measured by indirect calorimetry using an open circuit calorimetry system (Oxymax, Columbus Instruments Int. Corp., USA). RQ is the ratio of the volume of CO<sub>2</sub> produced (VCO<sub>2</sub>) to the volume of O<sub>2</sub> consumed (VO<sub>2</sub>). EE was calculated as the product of calorific value of oxygen (CV) and VO<sub>2</sub> per kilogram of body weight, where CV = 3.815 + 1.232 (RQ). Total calories expended were calculated to determine daily fuel utilization. To calculate the proportion of protein, fat and carbohydrate that is used during that 24-hour period, we used Flatt's proposal (see, Flatt JP 1991 Assessment of daily and cumulative carbohydrate and fat balances in mice. J Nutr Biochem 2:193-202.) and formulae as well as other derived constants (see Elia M, Livesey G 1992 Energy expenditure and fuel selection in biological systems: the theory and practice of calculations based on indirect calorimetry and tracer methods. World Rev Nutr Diet 70:68-131.). Food consumption over the 24-hour period was also measured. The minimum effective dose (MED) for inhibition of food consumption is reported as the lowest dose that caused a reduction in food consumption that was significantly different from vehicle treated controls. Results obtained for a sample of compounds of the invention with the indirect calorimetry assay are shown below in Table 4.

Table 4

Compound of Example	Inhibition of Feeding	Energy Balance*
	Diet Induced Obese Rat	Diet Induced Obese Rat
	Minimum Effective Dose (MED) mg/kg, p.o.	test dose 3 mg/kg, p.o. kcal/kg/day
290	3	-65
227	0.3	-68
228	0.3	-81

271	0.3	-35
263	$\leq 3$	-56
309	$\leq 3$	-39
253	$\leq 3$	-19
LY255582	1	-36
Naltrexone®	>10	Not significant

\* Energy balance = caloric intake minus utilization (kcal/kg/day)

The indirect calorimetry assay above shows that the minimum effective dose to inhibit food consumption at a level significantly different from the level achieved with a vehicle control dose was comparable or better for compounds of the present invention compared to a reference compound.

### Formulation

A compound of the invention is preferably presented in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of the invention. Such compositions will contain from about 0.1 percent by weight to about 90.0 percent by weight of the compound of the invention (Active Ingredient). As such, the present invention also provides pharmaceutical formulations comprising a compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient thereof.

In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material that acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), and soft and hard gelatin capsules.

Examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin,

syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

For oral administration, the Active Ingredient, a compound of this invention, may be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the Active Ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

In order to more fully illustrate the operation of this invention, the following formulation examples are provided. The examples are illustrative only, and are not intended to limit the scope of the invention. The formulations may employ as Active Ingredient any of the compounds of the present invention.

#### FORMULATION I

Hard gelatin capsules are prepared using the following ingredients:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Active Ingredient	250	55
Starch dried	200	43
Magnesium stearate	10	2

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

**FORMULATION 2**

Capsules each containing 20 mg of medicament are made as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Active Ingredient	20	10
Starch	89	44.5
Microcrystalline cellulose	89	44.5
Magnesium stearate	2	1

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

**FORMULATION 3**

Capsules each containing 100 mg of active ingredient are made as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Active Ingredient	100	30
Polyoxyethylene Sorbitan monooleate	50mcg	0.02
Starch powder	250	69.98

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

## FORMULATION 4

Tablets each containing 10 mg of active ingredient are prepared as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Active Ingredient	10	10
Starch	45	45
Microcrystalline cellulose	35	35
Polyvinylpyrrolidone (as 10% solution in water)	4	4
Sodium carboxymethyl starch	4.5	4.5
Magnesium stearate	0.5	0.5
talc	1	1

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50-60 °C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules, which after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

## FORMULATION 5

A tablet formula may be prepared using the ingredients below:

Compound	Amount per capsule (mg)	Percent by weight (%)
Active Ingredient	250	38
Cellulose microcrystalline	400	60
Silicon dioxide fumed	10	1.5



Stearic acid	5	0.5
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The components are blended and compressed to form tablets each weighing 665mg.

#### FORMULATION 6

Suspensions each containing 5 mg of medicament per 5 ml dose are made as follows:

Compound	Amount per 5mL suspension (ml)
Active Ingredient	5
Sodium carboxymethyl cellulose	50
Syrup	1.25
Benzoic acid solution	0.10
Flavor	q.v.
Color	q.v.
Water	q.s. to 5mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the paste with stirring. Sufficient water is then added to produce the required volume.

#### FORMULATION 7

An aerosol solution is prepared containing the following components:

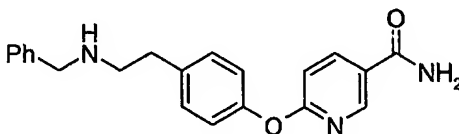
Compound	Concentration by weight (percent)
Active Ingredient	0.25
Ethanol	29.75
Propellant 22	70.0

(chlorodifluoromethane)	
-------------------------	--

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.

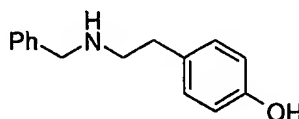
### Example 1

6-[4-(2-Benzylamino-ethyl)-phenoxy]-nicotinamide



#### Step 1

4-(2-Benzylamino-ethyl)-phenol



Add benzaldehyde (7.5 mL, 74 mmol) to a stirred solution of tyramine (10.00 g, 73 mmol) and anhydrous methanol (90 mL). Heat reaction to reflux for 1 h under nitrogen. Cool reaction to 0 °C and slowly add sodium borohydride (2.84 g, 75 mmol). Stir for 1 h at room temperature and then concentrate on a rotary evaporator. Add water (100 mL) and stir for 1.5 h at room temperature. Filter and wash with water to yield 10.11 g (61%) of 4-(2-benzylamino-ethyl)-phenol: mass spectrum (ion spray):  $m/z$  = 228.1(M+1);  $^1\text{H}$  NMR (DMSO- $d_6$ ): 9.14 (br s, 1H), 7.29-7.18 (m, 5H), 6.96 (d, 2H), 6.65 (d, 2H), 3.69 (s, 2H), 2.67-2.60 (m, 4H), 2.02 (br s, 1H).

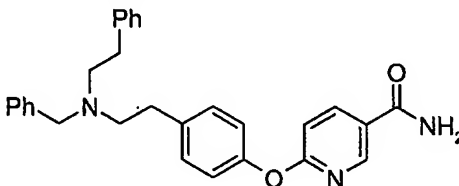
#### Step 2

Add 6-chloronicotinamide (7.03 g, 44.90 mmol) to a stirred solution of 4-(2-benzylamino-ethyl)-phenol (10.10 g, 44.43 mmol), potassium carbonate (15.35 g, 111.1 mmol), dimethylacetamide (138 mL), and isooctane (16 mL). Using a Dean-Stark trap, heat the reaction to reflux under nitrogen for 6 h. Cool the reaction mixtures to room

temperature, filter off the solids, and concentrate most of the solvent off on a rotary evaporator. Take the residue up in ethyl acetate (200 mL) and add 1N hydrochloric acid (200 mL). Stir for 15 minutes and filter off the precipitate washing with ethyl acetate. Dissolve the solid in 400 mL of boiling 1:1 methanol/water. To this solution add 5N sodium hydroxide (35 mL) and allow the solution to cool to room temperature. Filter and wash with water to yield 19.74 g (83%) of 6-[4-(2-benzylamino-ethyl)-phenoxy]-nicotinamide: mass spectrum (ion spray):  $m/z = 348.1(M+1)$ ;  $^1H$  NMR ( $CDCl_3$ ): 8.58 (d, 1H), 8.15 (dd, 1H), 7.34-7.24 (m, 7H), 7.06 (d, 2H), 6.93 (d, 1H), 6.08 (br s, 2H), 3.82 (s, 2H), 2.92 (t, 2H), 2.84 (t, 2H), 1.33 (br s, 1H).

### Example 2

#### 6-{4-[2-(Benzyl-phenethyl-amino)-ethyl]-phenoxy}-nicotinamide



Add sodium bicarbonate (0.0823 g, .0980 mmol) to a stirred solution of 6-[4-(2-benzylamino-ethyl)-phenoxy]-nicotinamide (0.3061 g, .0881 mmol), (2-bromoethyl)benzene (0.135 mL, 0.988 mmol), and DMF (5 mL). Heat the reaction to reflux for 3 h under nitrogen and then cool to room temperature. Pour the reaction into water (50 mL) and extract with diethyl ether (3 X 50 mL). Dry the diethyl ether extracts over magnesium sulfate and then filter off the magnesium sulfate. Concentrate on a rotary evaporator and purify the crude product by flash chromatography on silica gel eluting with 90% ethyl acetate / hexanes to yield 0.1538 g (39%) of 6-{4-[2-(benzyl-phenethyl-amino)-ethyl]-phenoxy}-nicotinamide: mass spectrum (ion spray):  $m/z = 452.1(M+1)$ ;  $^1H$  NMR ( $CDCl_3$ ): 8.55 (d, 1H), 8.13 (dd, 1H), 7.29-7.11 (m, 14H), 7.01 (d, 2H), 6.92 (d, 1H), 3.71 (s, 1H), 2.94-2.77 (m, 9H).

By the method of example 1 the following compounds were prepared:

Example	Name	Mass spectrum (ion spray): $m/z$	$^1H$ NMR ( $CDCl_3$ )

		(M+1)	
3	6-(4-{2-[Benzyl-(3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide	466.1	8.53 (d, 1H), 8.11 (dd, 1H), 7.29-7.11 (m, 14H), 7.03-7.00 (m, 2H), 6.91 (d, 1H), 3.63 (s, 2H), 2.77-2.68 (m, 4H), 2.59-2.52 (m, 4H), 1.83-1.75 (m, 2H)
4	6-{4-[2-(Benzyl-hexyl-amino)-ethyl]-phenoxy}-nicotinamide	433.1	8.56 (d, 1H), 8.13 (dd, 1H), 7.29-7.15 (m, 9H), 7.01 (d, 2H), 6.92 (dd, 1H), 3.62 (s, 2H), 2.78-2.66 (m, 4H), 2.48 (t, 2H), 1.48-1.43 (m, 2H), 1.30 - 1.23 (m, 6H), 0.86 (t, 3H)
5	6-{4-[2-(Benzyl-heptyl-amino)-ethyl]-phenoxy}-nicotinamide	446.2	8.56 (d, 1H), 8.13 (dd, 1H), 7.31-7.15 (m, 7H), 7.01 (d, 2H), 6.91 (d, 1H), 5.85 (br s, 2H), 3.62 (s, 2H), 2.78-2.66 (m, 4H), 2.48 (t, 2H), 1.48-1.45 (m, 2H), 1.29-1.24 (m, 8H), 0.86 (t, 3H)
6	6-(4-{2-[Benzyl-(5-methyl-hexyl)-amino]-ethyl}-phenoxy)-nicotinamide	446.1	8.55 (dd, 1H), 8.13 (dd, 1H), 7.29-7.16 (m, 9H), 7.03-6.98 (m, 2H), 6.92 (dd, 1H), 3.62 (s, 2H), 2.78-2.67 (m, 4H), 2.48 (t, 2H), 1.52-1.41 (m, 3H), 1.29-1.21 (m, 2H), 1.15-1.10 (m, 2H), 0.84 (d, 6H)
7	6-[4-(2-{Benzyl-[2-(3-chloro-phenyl)-ethyl]-amino}-ethyl)-phenoxy]-nicotinamide	486.2	8.55 (dd, 1H), 8.14 (dd, 1H), 7.28-6.91 (m, 16H), 3.69 (s, 2H), 2.78-2.69 (m, 8H)
8	6-(4-{2-[Benzyl-(3-cyclohexyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide	472.2	8.55 (d, 1H), 8.13 (dd, 1H), 7.29-7.15 (m, 9H), 7.01 (d, 2H), 6.92 (d, 1H), 3.62 (s, 2H), 2.78-2.67 (m, 4H), 2.46 (t, 2H), 1.67-1.46 (m, 7H), 1.19-1.12 (m, 6H), 0.87-0.82 (m, 2H)
9	6-(4-{2-[Benzyl-(3-otolyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide	480.0	8.54 (d, 1H), 8.13 (dd, 1H), 7.31-7.00 (m, 15H), 6.93 (d, 1H), 3.67 (s, 2H), 2.78-2.74 (m, 4H), 2.62-2.55 (m, 4H), 2.28 (s, 3H), 1.80-1.73 (m, 2H)
10	6-(4-{2-[Benzyl-(3-	472.1	8.55 (dd, 1H), 8.14 (dd, 1H), 7.31-6.72

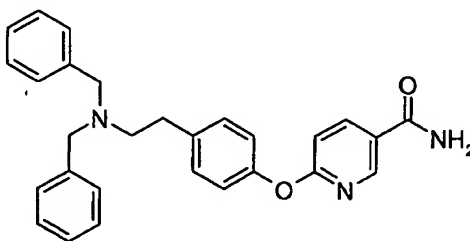
	thiophen-2-yl-propyl)- amino]-ethyl]-phenoxy)- nicotinamide		(m, 15H), 3.65 (s, 2H), 2.83-2.71 (m, 6H), 2.58 (t, 2H), 1.89-1.60 (m, 2H)
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By the method of example 2 the following compounds were prepared:

Example	Name	Data		
		Mass spectrum (ion spray): m/z (M+1)	HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB- Phenyl Column 4.6mmx15cmx5micron	
			Purity	Retention Time (minutes)
11	6-{4-[2-(Benzyl-pentyl- amino)-ethyl]-phenoxy}- nicotinamide	418.1	98.0	8.28
12	6-(4-{2-[Benzyl-(3- cyclopentyl-propyl)- amino]-ethyl]-phenoxy}- nicotinamide	458.4	96.6	8.94
13	6-[4-(2-{Benzyl-[2-(2- fluoro-phenyl)-ethyl]- amino}-ethyl)-phenoxy]- nicotinamide	470.3	98.0	8.44

#### Example 14

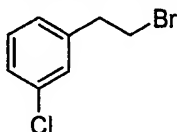
6-[4-(2-Dibenzylamino-ethyl)-phenoxy]-nicotinamide



Compound of Example 14 is prepared by the method of Example 2.

**Examples 15A-15E****Step 1**

1-(2-Bromo-ethyl)-3-chloro-benzene -



Add triphenylphosphine (3.90 g, 14.9 mmol) to a stirred solution of 3-chlorophenethyl alcohol (2.0 mL, 14.8 mmol), carbon tetrabromide (4.91 g, 14.8 mmol) and anhydrous dichloromethane (100 mL). Stir for 5 h under nitrogen at room temperature, and then wash with water (100 mL) and brine (100 mL). Dry the dichloromethane layer over magnesium sulfate, filter, and concentrate on a rotary evaporator to give the crude product. The crude product is purified by flash chromatography on silica gel eluting with 100% hexanes to yield 2.30 g (71%) of 1-(2-bromo-ethyl)-3-chloro-benzene: TLC:  $R_f$  in 100% hexanes: 0.27;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.26-7.11 (m, 3H), 7.09-7.07 (m, 1H), 3.54 (t, 2H), 3.12 (t, 2H).

**Step 2**

Add sodium triacetoxyborohydride (0.2600 g, 1.227 mmol) to a stirred solution of 6-[4-(2-benzylamino-ethyl)-phenoxy]-nicotinamide (0.3058 g, 0.8802 mmol), benzaldehyde (0.092 mL, 0.905 mmol), glacial acetic acid (0.052 mL, 0.908 mmol) and 1,2-dichloroethane (8 mL). Stir for 18 h at room temperature under nitrogen. Pour the reaction into 1N sodium hydroxide (50 mL) and extract with diethyl ether (3 X 50 mL). Wash the diethyl ether extracts with brine, dry over magnesium sulfate, filter, and concentrate on a rotary evaporator to give the crude product. The crude product is purified by flash chromatography on silica gel eluting with 75% ethyl acetate / hexanes to yield 0.2501 g (65%) of 6-[4-(2-dibenzylamino-ethyl)-phenoxy]-nicotinamide: HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron: Retention time: 8.14 minutes, Purity: 99.7%; mass spectrum (ion spray):  $m/z = 438.0(\text{M}+1)$ .

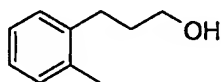
The following compounds (Examples 15A –15E) were prepared from the corresponding commercially available alcohols except examples 1-(3-bromo-propyl)-2-

methyl-benzene and 2-(3-bromo-propyl)-thiophene in which the starting alcohols were synthesized:

Example No.	Name	TLC: R <sub>f</sub> in 100% Hexanes	<sup>1</sup> H NMR (CDCl <sub>3</sub> )
15A	(3-Bromo-propyl)-cyclopentane	0.55	3.38 (t, 2H), 1.89-1.38 (m, 11H), 1.11-1.02 (m, 2H)
15B	(3-Bromo-propyl)-cyclohexane	0.55	3.37 (t, 2H), 1.87-1.81 (m, 2H), 1.69-1.59 (m, 5H), 1.31-1.06 (m, 6H), 0.91-0.83 (m, 2H)
15C	1-(2-Bromo-ethyl)-3-fluoro-benzene	0.28	7.30-7.24 (m, 1H), 6.98-6.89 (m, 3H), 3.55 (t, 2H), 3.15 (t, 2H)
15D	1-(3-Bromo-propyl)-2-methyl-benzene	0.22	7.17-7.12 (m, 4H), 3.45 (t, 2H), 2.78 (t, 2H), 2.33 (s, 3H), 2.17-2.10 (m, 2H)
15E	2-(3-Bromo-propyl)-thiophene	0.2	7.16-7.13 (m, 1H), 6.95-6.92 (m, 1H), 6.85-6.83 (m, 1H), 3.44 (t, 2H), 3.02 (t, 2H), 2.25-2.18 (m, 2H)

#### Preparing Alcohol Starting Material for Example 15D

##### 3-*o*-Tolyl-propan-1-ol

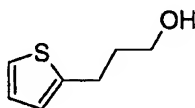


Add 2-methylhydrocinnamic acid (18.4 mmol) to anhydrous tetrahydrofuran (100 mL) and cool to 0 °C. Slowly add lithium aluminum hydride (2.20 g, 58.0 mmol) and remove the ice bath after 20 minutes. Stir at room temperature under nitrogen for 18 h. Cool the reaction to 0 °C and quench the reaction by slowly adding water (2.2 mL), 15% sodium hydroxide (2.2 mL), and water (6.6 mL). Filter off the aluminum salts. Add

brine (100 mL) and 5 N sodium hydroxide (30 mL) to the filtrate and extract with ethyl acetate (3 X 100 mL). Dry the ethyl acetate extracts with magnesium sulfate, filter, and concentrate on a rotary evaporator to yield 2.65 g (96%) of 3-o-tolyl-propan-1-ol:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.18-7.10 (m, 4H), 3.72 (t, 2H), 2.72-2.69 (m, 2H), 2.33 (s, 3H), 1.90-1.83 (m, 2H), 1.60 (br s, 1H).

#### Preparing Alcohol Starting Material for Example 15E

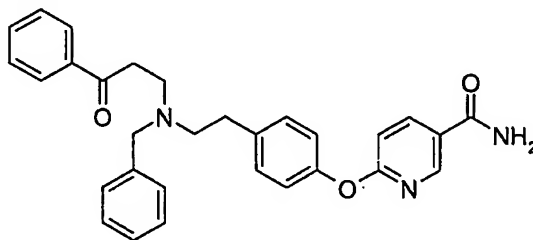
##### 3-Thiophen-2-yl-propan-1-ol



Using a method similar to example 15D, using 3-(2-thienyl)propanoic acid affords the title compound:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.12 (dd, 1H), 6.92 (dd, 1H), 6.82-6.80 (m, 1H), 3.70 (t, 2H), 2.96-2.92 (m, 2H), 1.98-1.91 (m, 2H), 1.67 (br s, 1H).

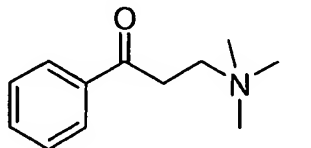
#### Example 16

##### 6-(4-{2-[Benzyl-(3-oxo-3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide



#### Step 1

##### 3-Trimethylammonium-1-phenyl-propan-1-one iodide



Add concentrated hydrochloric acid (0.090 mL, 1.1 mmol) to a stirred solution of acetophenone (5.0 mL, 43 mmol), paraformaldehyde (2.15 g), dimethylamine hydrochloride (4.54 g, 56 mmol), and ethanol (15 mL). Heat the reaction to reflux for 18



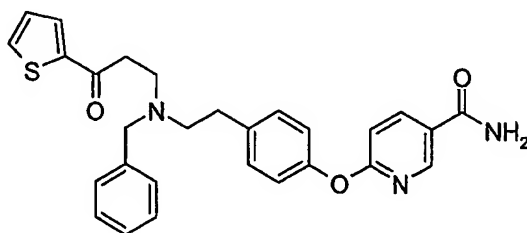
h under nitrogen. Cool the reaction to room temperature, pour it into 1 N sodium hydroxide (150 mL), and extract with diethyl ether (3 X 150 mL). Dry the diethyl ether extracts over magnesium sulfate, filter, and concentrate on a rotary evaporator to give the crude product. Dissolve the crude product in ethanol (70 mL) and add iodomethane (3.2 mL, 51 mmol). Stir the reaction at room temperature for 18 h under nitrogen. Filter and wash with ethanol followed by diethyl ether to yield 12.56 g (92%) of 3-trimethylammonium-1-phenyl-propan-1-one iodide: mass spectrum (ion spray):  $m/z = 193.0(M+1)$ ;  $^1H$  NMR (DMSO- $d_6$ ): 8.08-8.06 (m, 2H), 7.72-7.67 (m, 1H), 7.60-7.55 (m, 2H), 3.70 (s, 4H), 3.14 (s, 6H), 3.11 (s, 3H).

## Step 2

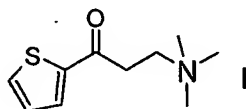
Add 3-trimethylammonium-1-phenyl-propan-1-one iodide (0.3612 g, 1.132 mmol) to a stirred solution of 6-[4-(2-benzylamino-ethyl)-phenoxy]-nicotinamide (0.3041 g, 0.8753 mmol), sodium carbonate (0.1862 g, 1.757 mmol), and dimethylformamide (5 mL). Bubble nitrogen through the reaction for 18 h at room temperature. Pour the reaction into 1 N sodium hydroxide (50 mL) and extract with diethyl ether (3 X 50 mL). Dry the diethyl ether extracts over magnesium sulfate, filter, and concentrate on a rotary evaporator to give the crude product. The crude product is purified by flash chromatography on silica gel eluting with 90% ethyl acetate / hexanes to yield 0.1910 g (46%) of 6-(4-{2-[benzyl-(3-oxo-3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide: mass spectrum (ion spray):  $m/z = 480.1(M+1)$ ;  $^1H$  NMR ( $CDCl_3$ ): 8.57 (d, 1H), 8.15 (dd, 1H), 7.90-7.88 (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.42 (m, 2H), 7.28-7.15 (m, 9H), 7.04-7.00 (m, 2H), 6.93 (d, 1H), 3.71 (s, 2H), 3.13-3.01 (m, 4H), 2.78 (s, 4H).

**Example 17**

6-(4-{2-[Benzyl-(3-oxo-3-thiophen-2-yl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide

**Step 1**

3-Trimethylammonium-1-thiophen-2-yl-propan-1-one iodide



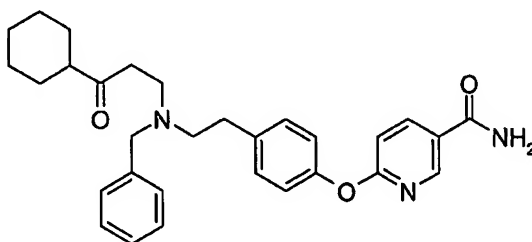
Using a method similar to example 16, using 2-acetylthiophene affords the title compound: mass spectrum (ion spray):  $m/z = 199.0(M+1)$ ;  $^1H$  NMR (DMSO- $d_6$ ): 8.12-8.04 (m, 2H), 7.32-7.28 (m, 1H), 3.70-3.61 (m, 4H), 3.11 (s, 6H), 3.09 (s, 3H).

**Step 2**

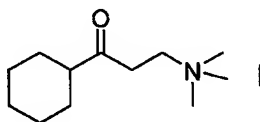
Using a method similar to example 16, using 3-trimethylammonium-1-thiophen-2-yl-propan-1-one iodide affords the title compound: mass spectrum (ion spray):  $m/z = 486.3(M+1)$ ;  $^1H$  NMR ( $CDCl_3$ ): 8.57 (d, 1H), 8.15 (dd, 1H), 7.63-7.60 (m, 2H), 7.29-7.01 (m, 12H), 6.93 (d, 1H), 3.71 (s, 2H), 3.04 (s, 4H), 2.78 (br s, 4H).

**Example 18**

6-(4-{2-[Benzyl-(3-cyclohexyl-3-oxo-propyl)-amino]-ethyl}-phenoxy)-nicotinamide

**Step 1**

1-Cyclohexyl-3-trimethylammonium-propan-1-one iodide



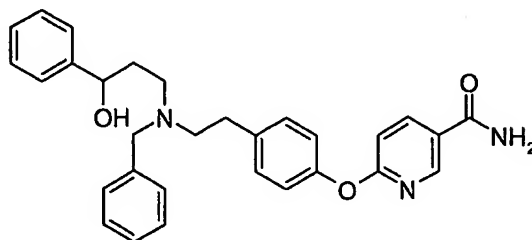
Using a method similar to example 16, using cyclohexyl methyl ketone affords the title compound: mass spectrum (ion spray):  $m/z = 198.2(M+1)$ ;  $^1H$  NMR (DMSO- $d_6$ ): 3.51-3.47 (m, 4H), 3.11 (s, 6H), 3.05 (s, 3H), 2.49-2.42 (m, 1H), 1.87-1.84 (m, 2H), 1.73-1.60 (m, 3H), 1.31-1.12 (m, 5H).

**Step 2**

Using a method similar to example 16, using 1-cyclohexyl-3-trimethylammonium-propan-1-one iodide affords the title compound. Mass spectrum (ion spray):  $m/z = 486.1(M+1)$ ;  $^1H$  NMR ( $CDCl_3$ ): 8.58 (d, 1H), 8.15 (dd, 1H), 7.31-7.15 (m, 9H), 7.04-7.01 (m, 2H), 6.93 (d, 1H), 3.63 (s, 2H), 2.87-2.57 (m, 8H), 2.30-2.24 (m, 1H), 1.81-1.64 (m, 5H), 1.33-1.15 (m, 5H).

**Example 19**

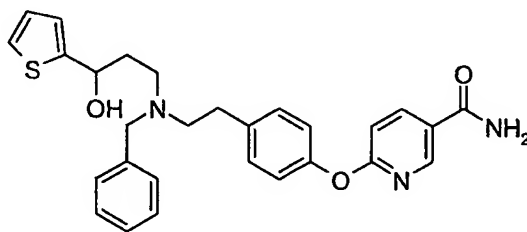
6-(4-{2-[Benzyl-(3-hydroxy-3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide



Add methanol (10 mL) to 6-(4-{2-[benzyl-(3-oxo-3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide (0.1871 g, 0.3901 mmol) and cool to 0 °C. Add sodium borohydride (0.0664 g, 1.756 mmol) and stir for 1.5 h at 0 °C under nitrogen. Pour the reaction into brine (50 mL) and extract with diethyl ether (3 X 50 mL). Dry the diethyl ether extracts over magnesium sulfate, filter, and concentrate on a rotary evaporator to give the crude product. The crude product is purified by flash chromatography on silica gel eluting with 100% ethyl acetate to yield 0.0239 g (13%) of 6-(4-{2-[benzyl-(3-hydroxy-3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide: HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron: Retention time: 8.07 minutes, Purity: 99.9%; mass spectrum (ion spray):  $m/z = 482.3(M+1)$ .

**Example 20**

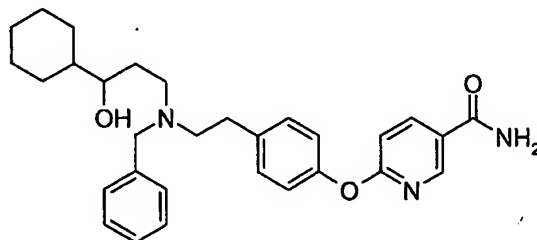
6-(4-{2-[Benzyl-(3-hydroxy-3-thiophen-2-yl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide



Using a method similar to example 19, using 6-(4-{2-[benzyl-(3-oxo-3-thiophen-2-yl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide affords the title compound: HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron: Retention time: 7.93 minutes, Purity: 99.2%; mass spectrum (ion spray):  $m/z = 488.0(M+1)$ .

**Example 21**

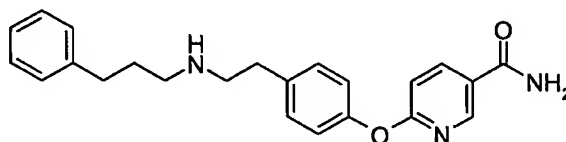
6-(4-{2-[Benzyl-(3-cyclohexyl-3-hydroxy-propyl)-amino]-ethyl}-phenoxy)-nicotinamide



Using a method similar to example 19, using 6-(4-{2-[benzyl-(3-cyclohexyl-3-oxo-propyl)-amino]-ethyl}-phenoxy)-nicotinamide affords the title compound: HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron: Retention time: 8.49 minutes, Purity: 99.0%; mass spectrum (ion spray):  $m/z = 488.1(M+1)$ .

**Example 22**

6-{4-[2-(3-Phenyl-propylamino)-ethyl]-phenoxy}-nicotinamide



Add 1-chloroethylchloroformate (0.056 mL, 0.52 mmol) to a stirred solution of 6-(4-{2-[benzyl-(3-phenyl-propyl)-amino]-ethyl}-phenoxy)-nicotinamide (0.1211 g, 0.2603 mmol) (Example 3) and 1,2-dichloroethane (5 mL). Heat the reaction to reflux under nitrogen for 1.5 h. Add methanol (7 mL) and heat at reflux under nitrogen for 1 h. Cool the reaction to room temperature and add 2 M ammonia in methanol (5 mL). Concentrate on a rotary evaporator to give the crude product. The crude product is purified by flash chromatography on silica gel eluting with 1% concentrated ammonium hydroxide / 10% ethanol / chloroform to yield 0.0654 g (67%) of 6-{4-[2-(3-phenyl-propylamino)-ethyl]-phenoxy}-nicotinamide: HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron: Retention time: 7.48 minutes, Purity: 99.2%; mass spectrum (ion spray):  $m/z = 376.2(M+1)$ .

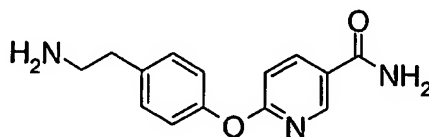
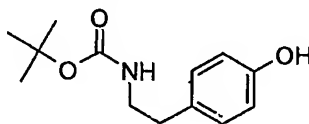
By the method of example 22 the following compounds were prepared from the corresponding compounds prepared in examples 2-14:

Example	Name	Data		
		Mass spectrum (ion spray): m/z (M+1)	HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron)	
			Purity	Retention Time (minutes)
23	6-[4-(2-Phenethylamino-ethyl)-phenoxy]-nicotinamide	362.1	98.9	5.28
24	6-[4-(2-Hexylamino-ethyl)-phenoxy]-nicotinamide	342.1	99.2	7.01
25	6-[4-(2-Heptylamino-ethyl)-phenoxy]-nicotinamide	356.2	99.8	8.13
26	6-[4-(2-Pentylamino-ethyl)-phenoxy]-nicotinamide	328.1	98.7	4.44
27	6-{4-[2-(5-Methyl-hexylamino)-ethyl]-phenoxy}-nicotinamide	356.1	99.9	7.78
28	6-(4-{2-[2-(3-Chloro-phenyl)-ethylamino]-ethyl}-phenoxy)-nicotinamide	396.0	99.3	7.71
29	6-{4-[2-(3-Cyclopentyl-propylamino)-ethyl]-phenoxy}-nicotinamide	368.2	98.4	7.99
30	6-{4-[2-(3-Cyclohexyl-propylamino)-ethyl]-phenoxy}-nicotinamide	382.1	98.1	8.29
31	6-(4-{2-[2-(3-Fluoro-phenyl)-ethylamino]-ethyl}-phenoxy)-	380.1	99.1	1.43

	nicotinamide			
32	6-{4-[2-(3-o-Tolyl-propylamino)-ethyl]-phenoxy}-nicotinamide	390.1	99.1	7.88
33	6-{4-[2-(3-Thiophen-2-yl-propylamino)-ethyl]-phenoxy}-nicotinamide	382.1	98.6	5.4

**Example 34**

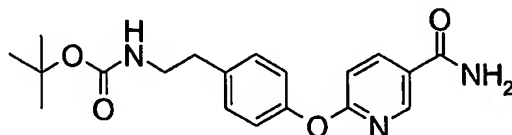
6-[4-(2-Amino-ethyl)-phenoxy]-nicotinamide

**Step 1**[2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester

Add di-*tert*-butyl dicarbonate (9.75 g, 44.7 mmol) to a stirred solution of tyramine (5.00 g, 36.5 mmol) and anhydrous tetrahydrofuran. Stir the reaction at room temperature for 18 h under nitrogen. Concentrate the reaction to give the crude product. The crude product is purified by flash chromatography on silica gel eluting with 35% ethyl acetate / hexanes to yield 7.56 g (87%) of [2-(4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester: mass spectrum (ion spray):  $m/z = 236.1$  (M-1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.01 (d, 2H), 6.77 (d, 2H), 6.10 (br s, 1H), 4.61 (br s, 1H), 3.34-3.32 (m, 2H), 2.72-2.68 (m, 2H), 1.44 (s, 9H).

## Step 2

{2-[4-(5-Carbamoyl-pyridin-2-yloxy)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester



Add potassium *tert*-butoxide (4.28 g, 36.2 mmol) to a stirred solution of [2-(4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (6.40 g, 27.0 mmol) and anhydrous tetrahydrofuran (120 mL). Stir for 30 minutes under nitrogen at room temperature. Add 6-chloronicotinamide (4.27 g, 27.2 mmol) and heat to reflux for 18 h under nitrogen. Cool to room temperature, pour the reaction mixture into brine (150 mL), and extract with diethyl ether (3 X 150 mL). Dry the diethyl ether extracts over magnesium sulfate, filter, and concentrate on a rotary evaporator to give the crude product. The crude product is purified by flash chromatography on silica gel eluting with 0.7% concentrated ammonium hydroxide / 7% ethanol / chloroform to yield 4.46 g (46%) of {2-[4-(5-carbamoyl-pyridin-2-yloxy)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester: mass spectrum (ion spray):  $m/z = 358.1(M+1)$ ;  $^1H$  NMR (DMSO- $d_6$ ): 8.58 (d, 1H), 8.22 (dd, 1H), 8.02 (br s, 1H), 7.46 (br s, 1H), 7.23 (d, 2H), 7.06-7.02 (m, 3H), 6.92-6.89 (m, 1H), 3.17-3.12 (m, 2H), 2.69 (t, 2H), 1.35 (s, 9H).

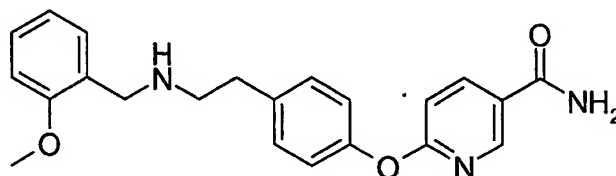
## Step 3

Add dichloromethane (60 mL) to the compound of Example 33 Step 2 (5.12 g, 14.3 mmol). To this slurry add trifluoroacetic acid (32.0 mL, 415 mmol) and stir under nitrogen for 1.5 h. Divide the reaction into three equal aliquots and load each aliquot onto a 10 g prepacked SCX cartridge. Wash with methanol (200 mL) and elute the product off the cartridge with 2 M ammonia in methanol (100 mL). Combine the 2 M ammonia in methanol washes from the three cartridges and concentrate on a rotary evaporator to give 3.11 g (84%) of 6-[4-(2-amino-ethyl)-phenoxy]-nicotinamide: mass spectrum (ion spray):  $m/z = 258.1(M+1)$ ;  $^1H$  NMR (DMSO- $d_6$ ): 8.61 (d, 1H), 8.25 (dd, 1H), 8.04 (s, 1H), 7.49 (s, 1H), 7.30-7.23 (m, 2H), 7.11-7.03 (m, 3H), 2.80-2.63 (m, 4H), 1.89 (br s, 2H).



## Example 35

6-{4-[2-(2-Methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide



Add three-angstrom molecular sieves to a stirred solution of 6-[4-(2-amino-ethyl)-phenoxy]-nicotinamide (0.1000 g, 0.3887 mmol) (compound of example 33), 2-methoxybenzaldehyde (0.047 mL, 0.39 mmol), and methanol (5 mL). Agitate the reaction for 18 h on a platform shaker at room temperature. Add sodium borohydride and agitate for 1 h at room temperature. Filter to remove the molecular sieves and load the reaction mixture directly onto a 10 g prepacked SCX cartridge. Flush with methanol (150 mL) and elute the product off the SCX cartridge with 2 M ammonia in methanol (50 mL). Concentrate on a rotary evaporator to give 0.1253 g (85%) of 6-{4-[2-(2-methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide: HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron: Retention time: 4.14 minutes, Purity: 97.9%; mass spectrum (ion spray):  $m/z = 378.1(M+1)$ .

By the method of example 34 the following compounds were prepared:

Example	Name	Data		
		Mass spectrum (ion spray): $m/z$ (M+1)	HPLC (30/70 to 90/10 ACN/(0.1%TFA in water) Zorbax SB-Phenyl Column 4.6mmx15cmx5micron	
			Purity	Retention Time (minutes)
36	6-{4-[2-(3-Fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide	366.1	99.0	3.69
37	6-{4-[2-(3-Chloro-benzylamino)-ethyl]-phenoxy}-nicotinamide	382.0	99.2	5.22

38	6-{4-[2-(3,4-Dichloro-benzylamino)-ethyl]-phenoxy}-nicotinamide	416.0	99.0	7.73
39	6-{4-[2-(3-Trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	416.1	99.1	7.52
40	6-{4-[2-(4-Cyano-benzylamino)-ethyl]-phenoxy}-nicotinamide	373.1	90.8	3.00
41	6-{4-[2-(4-Fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide	366.1	100.0	3.76
42	6-{4-[2-(4-Methyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	362.1	98.6	4.92
43	6-{4-[2-(3,5-Bis-trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	484.0	98.7	8.30
44	6-{4-[2-(2,6-Difluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide	384.1	100.0	3.13
45	6-{4-[2-(3,5-Difluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide	384.1	98.4	4.25
46	6-{4-[2-(4-Acetylamino-benzylamino)-ethyl]-phenoxy}-nicotinamide	405.1	99.3	2.12
47	6-{4-[2-(2-Trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	416.1	99.1	5.87
48	6-{4-[2-(2-Methyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	362.1	98.7	4.13
49	6-{4-[2-(3-Methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	378.1	98.5	3.70

50	6-{4-[2-(4-Chloro-benzylamino)-ethyl]-phenoxy}-nicotinamide	382.0	99.4	5.11
51	6-{4-[2-(4-Phenoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	440.1	99.4	8.19
52	6-{4-[2-(4-Methoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	378.1	98.7	3.56
53	6-{4-[2-(4-Trifluoromethyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	416.1	99.4	7.46
54	6-{4-[2-(3-Oxo-2,3-dihydro-1H-isoindol-1-ylamino)-ethyl]-phenoxy}-nicotinamide	389.1	95.8	2.05
55	6-{4-[2-(4-Trifluoromethoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	432.1	99.5	7.79
56	6-{4-[2-(3-Trifluoromethoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	432.1	99.3	7.72
57	6-(4-{2-[(Thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	354.0	99.1	2.63
58	6-(4-{2-[(Furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	338.1	99.0	2.27
59	6-[4-(2-Octylamino-ethyl)-phenoxy]-nicotinamide	370.2	96.7	8.34
60	6-[4-(2-Cyclohexylamino-ethyl)-phenoxy]-nicotinamide	340.2	90.4	3.04
61	6-{4-[2-(Cyclohexylmethyl-amino)-ethyl]-phenoxy}-nicotinamide	354.2	98.7	5.10

62	6-[4-(2-Propylamino-ethyl)-phenoxy]-nicotinamide	300.1	96.8	2.07
63	6-[4-(2-Butylamino-ethyl)-phenoxy]-nicotinamide	314.1	97.3	2.57
64	6-[4-(2-Isopropylamino-ethyl)-phenoxy]-nicotinamide	300.1	83.0	1.99
65	6-[4-(2-Isobutylamino-ethyl)-phenoxy]-nicotinamide	314.1	97.0	2.40
66	6-{4-[2-(3-Methyl-butylamino)-ethyl]-phenoxy}-nicotinamide	328.2	98.1	3.44
67	6-(4-{2-[(Pyridin-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	349.1	96.8	1.54
68	6-(4-{2-[(Pyridin-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	349.1	84.4	2.07
69	6-(4-{2-[(5-Methyl-furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	352.1	98.5	2.98
70	6-(4-{2-[(3-Methyl-thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	368.1	93.8	3.45
71	6-(4-{2-[(5-Methyl-thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	368.1	97.9	3.80
72	6-(4-{2-[(Thiophen-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	354.1	98.5	2.80
73	6-[4-(2-Ethylamino-ethyl)-phenoxy]-nicotinamide	286.1	100.0	2.43
74	6-{4-[2-(4-Hydroxy-benzylamino)-ethyl]-phenoxy}-	364.2	98.9	2.42

	nicotinamide			
75	6-{4-[2-(3-Hydroxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	364.2	99.4	2.43
76	6-{4-[2-(3-Phenyl-prop-2-ynylamino)-ethyl]-phenoxy}-nicotinamide	372.2	96.9	6.41
77	6-(4-{2-[(Furan-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	338.2	99.7	2.47
78	6-(4-{2-[(Benzofuran-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	388.2	98.4	5.48
79	6-(4-{2-[(5-Ethyl-furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	366.2	99.2	4.62
80	6-(4-{2-[(5-Chloro-thiophen-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	388.1	99.1	4.54
81	6-(4-{2-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	366.2	99.8	4.51
82	6-(4-{2-[(4-Chloro-1-methyl-1H-pyrazol-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	386.1	99.6	2.42
83	6-(4-{2-[(Thiazol-2-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	355.1	87.4	2.02
84	6-(4-{2-[(2-Methyl-1H-imidazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	352.2	100.0	100.00

85	6-{4-[2-(3,5-Di-tert-butyl-4-hydroxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	476.2	88.0	8.77
86	6-{4-[2-(2-Fluoro-benzylamino)-ethyl]-phenoxy}-nicotinamide	366.1	98.3	3.21
87	6-{4-[2-(3-Phenoxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	440.1	94.1	8.20
88	6-{4-[2-(2-Chloro-benzylamino)-ethyl]-phenoxy}-nicotinamide	382.0	91.3	4.04
89	6-{4-[2-(3-Cyano-benzylamino)-ethyl]-phenoxy}-nicotinamide	373.1	96.4	3.25
90	6-{4-[2-(3-Methyl-benzylamino)-ethyl]-phenoxy}-nicotinamide	362.1	92.8	4.80
91	6-(4-{2-[(1H-Imidazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	338.1	90.5	1.53
92	6-(4-{2-[(Pyridin-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	349.1	95.5	1.56
93	6-{4-[2-(2-Phenoxy-ethylamino)-ethyl]-phenoxy}-nicotinamide	378.1	85.7	4.67
94	6-{4-[2-(3-Fluoro-4-hydroxy-benzylamino)-ethyl]-phenoxy}-nicotinamide	382.0	83.3	2.49
95	6-(4-{2-[(2-Butyl-1H-imidazol-4-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	394.1	94.2	1.60
96	6-(4-{2-[(Benzo[b]thiophen-3-ylmethyl)-amino]-ethyl}-phenoxy)-nicotinamide	404.0	89.1	6.70